FACULTY OF HEALTH AND MEDICAL SCIENCES
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Rheumatoid Arthritis and Work

Risk and Risk Factors for Long Term Sickness Absence, Unemployment, and Disability Pension

PhD thesis

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Abbreviations

ACPA	Anti−citrullinated protein antibody
ASES	Arthritis Self-Efficacy Scale
bDMARDs	Biologic disease-modifying anti-rheumatic drugs
COPSOQ I/II	Copenhagen Psycho-Social Questionnaire version I and II
CPR	The central person register [Det Centrale Personregister]
CRP	C-reactive protein
csDMARDs	Conventional synthetic disease-modifying anti-rheumatic drugs
DANBIO	The Danish Rheumatologic Database
DANES	The Danish National Working Environment Cross-sectional Study
DISCO-08	Danish version of the International Standard of Classification of Occupations from 2008
DISCO-88	Danish version of the International Standard of Classification of Occupations from 1988
DMARDs	Disease-modifying anti-rheumatic drugs
DREAM	The Danish Register of the Evaluation of Marginalization
DWECS	Danish Work Environment Cohort Study
HR	Hazard ratio
ICD-10	International Classification of Diseases codes version 10
ICD-8	International Classification of Diseases codes version 8
ICF	International Classification of Functioning, Disability and Health
ICIDH	International Classification of Impairments, Disability and Handicaps
IgM-RF	Immunoglobulin M rheumatoid factor
KSQ	Karolinska Sleep Scale/questionnaire
LTSA	Long term sickness absence
MTX	Methotrexate
NPR	National Patient Register
NRCWE	National Research Centre for the Working Environment
PRESCRIBE	Danish National Prescription Registry
PY	Person years
RA	Rheumatoid Arthritis
RF	Serum rheumatoid factor
sDMARDs	Synthetic disease-modifying anti-rheumatic drugs

SF-36v2	The Short Form -36 version 2
WHO	World Health Organization

Papers

The present PhD study is based on the following papers, which will be referred to in the text as Paper I, Paper II and Paper III, respectively. The full papers are enclosed as Appendices I, II and III.

Paper I

Hansen SM, Hetland ML, Pedersen J, Østergaard M, Rubak TS, Bjorner JB.

Impact of Rheumatoid Arthritis on Long Term Sickness Absence in 1994-2011: A Danish Cohort Study.

J Rheumatology. in press.

Paper II

Hansen SM, Hetland ML, Pedersen J, Østergaard M, Rubak TS, Bjorner JB.

Impact of Rheumatoid Arthritis on Work Ability: A Register Study on the Prospective Risk of Long Term Sickness Absence, Unemployment, and Disability Pension, and the Probability for Return to Work.

Submitted

Paper III

Hansen SM, Hetland ML, Pedersen J, Østergaard M, Bjorner JB.

Work Environmental Risk Factors for Long Term Sickness Absence in Patients with Rheumatoid Arthritis - A Two Year Prospective Cohort Study

Submitted

Introduction

A large challenge for the Danish society in the years to come is to improve the retention of people on the labour market. Due to the aging work force, more and more employees will have to live with one or more chronic illnesses. Although medical treatment options in general continue to improve, the typical therapy of chronic diseases targets symptoms and functions rather than cures the patients. Thus, it is important to identify ways to prevent reduced work ability, and to help the employees who already have reduced work ability to keep their job.

This PhD study focuses on a serious inflammatory rheumatic disease, rheumatoid arthritis (RA). About 35,000 Danes are living with RA and approximately 1,700 people get diagnosed each year[1]. Disease onset may occur at any age, but the incidence is highest in individuals of 40 and 50 years of age.

RA has large impact on the patient's physical function and somatic and mental health, which makes long term sickness absence (LTSA), unemployment and early retirement important outcomes, both from an individual and a societal perspective. For the individual, LTSA often leads to reduced income and loss of contact with colleagues. Further, the individual has higher risk for permanent exclusion from the labor market. From a societal perspective, LTSA, unemployment and early retirement represent a significant loss of production and a substantial economic burden[2;3;4].

Aims

Main aim

The overall aim of the present PhD project was to study risk and risk factors for LTSA, unemployment, and disability pension in RA patients in Denmark.

The main aim was investigated in two cohort studies:

- A: a register study (Paper I and II) including 6,677 patients who were diagnosed with RA between year 1994 and 2011 and followed up until April 1st 2011 (Cohort A)
- B: a questionnaire study (Paper III) including 895 patients with RA, aged 18-59 years by May 1st 2010, and working, who responded to a questionnaire in 2011 and were followed up in registers for two years (Cohort B).

Specific aims

The main aim involved the following specific aims.

1) To estimate the relative risk of LTSA compared to the general population (Paper I+II).
2) To examine changes in the relative risk of LTSA over time (Paper I+II).
3) To evaluate the impact of other risk factors (e.g. physical work demands, age, gender, education, comorbidities) on LTSA (Paper I).
4) To estimate the relative risks of unemployment and disability pension, as well as the chance of return to work compared to the general population (Paper II).
5) To examine changes in the relative risks over time for unemployment and disability pension as well as the chance of return to work (Paper II).
6) To identify individual and work related risk factors for LTSA (self-reported physical functioning, psychosocial and physical working environment factors) (Paper III).

Background

Rheumatoid arthritis

RA is a chronic inflammatory disease, which has large impact on the patient's physical function and somatic and mental health. Of the there are 35,000 RA patients in Denmark[1], two-thirds of the patients are women and two thirds are at working age (<65 years)[5] and therefore at risk of long term sickness absence (LTSA), unemployment and early retirement.

The aetiology and pathogenesis of RA is complex, and genetic, individual and environmental factors are risk factors of RA. The main feature of RA is inflammation in a symmetrical pattern primarily located to the small synovial joints (e.g. the joints of hands, fingers, and toes), but any synovial joint may be involved. Patients with RA have swollen, painful, and stiff joints leading to impaired functional status, and in addition to this, they may also experience symptoms such as fatigue, low-grade fever and loss of weight[1]. The muscle and joint stiffness is usually worst in the morning or after extended periods of inactivity. In many patients, the joint inflammation leads to debilitating loss of cartilage, bone erosions, and joint deformity. As RA may result in irreversible joint damage early in the disease course, focus is on early diagnosis and treatment. Therefore, the classification criteria for RA from 1987[6] were replaced with new classification criteria in 2010[7]. Currently, both sets of criteria are in use. The classification criteria include e.g. anamnestic information, examination of the joints for inflammation and tenderness, and blood tests for auto-antibodies (anti-cyclic citrullinated peptide antibodies (ACPA) and IgM-rheumatoid factor (IgM-RF)), and serum C-reactive protein (CRP)[7]. Rheumatoid factor (RF) is present in about 60% to 78% of RA patients[8;9] and is a risk factor for more aggressive disease.

The anchor drug in the treatment of RA is methotrexate (MTX)[7]. It is prescribed as monotherapy or in combination with other synthetic disease-modifying anti-rheumatic drugs (sDMARDs) e.g. sulphasalazine or hydroxychlorochine. MTX and other sDMARDs have been shown to reduce inflammation and erosive progression[10;11]. They are, however, slow-acting, i.e. it takes 2-3 months before the effect is observed. Therefore, glucocorticoids (e.g. prednisolone) are used as bridging therapy, because they are fast-acting and have some disease-modifying effect[10;11]. Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, which are used for pain relief on demand, have no impact on the disease course. By year 2000, so-called biological disease-modifying anti-

rheumatic drugs (bDMARDs) were marketed. They block specific steps in the inflammatory process, are very effective, but also with increased risk of serious infections and other severe adverse effects. Furthermore, they are very expensive. In the national guidelines for RA, biological drugs are therefore only used as second line DMARD[1;12;13].

Until around year 2000, the treatment approach for patients with RA was based on the assumption that RA was a benign condition (not causing death or serious injury), and that the sDMARDs (of which intramuscular gold was the main drug) were very toxic. Therefore, sDMARD treatment was often first initiated after erosions had occurred. Modern treatment strategies in RA have developed since year 2000. They involve early diagnosis, close monitoring of disease activity, and early and aggressive treatment aiming at remission (i.e. suppression of joint symptoms) and prevention of erosions through the use of synthetic and biologic DMARDs[14].

A conceptual framework for the relation between RA and work related outcomes

Modern treatment strategies are not only aiming at remission and sustained remission but also aim to improve the RA patient's quality of life and participation in work and other everyday activities. Being able to maintain a job is important to the individual, to the family and for society as a whole[15]. Thus, in recent years, work related outcomes such as LTSA, unemployment, and disability pension have gained increased interest as relevant scientific outcomes for RA patients, as RA has important impact on work ability[15-19]. However, many other factors are also important and a comprehensive framework for understanding the impact of RA needs to include both environmental factors and personal factors[16;19-21]. The World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF)[22] offer such a framework.

The first attempt by the WHO to classify consequences of disease, the International Classification of Impairments, Disability and Handicap (ICIDH) was published in 1980[23]. The model and the definitions of impairment, disability and handicap are shown in Figure 1.

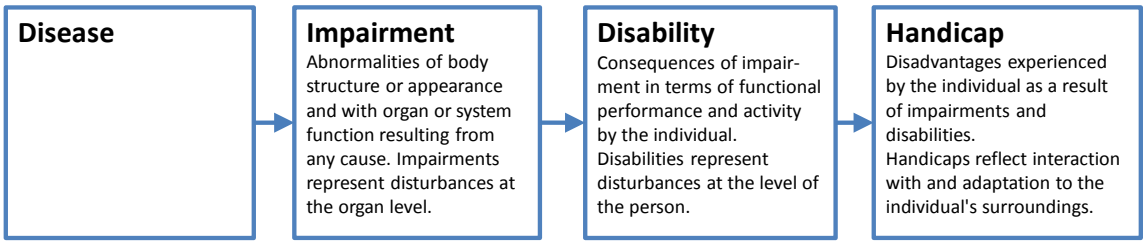

Figure 1. The International Classification of Impairments, Disability and Handicap (ICIDH) model[23]

The ICIDH represented a breakthrough in WHO thinking by recognizing that the standard medical model did not address the consequences of chronic diseases[24]. However, the ICIDH was criticized for not explicitly recognizing the role of the environment in its model and for its use of negative terminology[24]. The ICF addressed these criticisms[23] by incorporating environmental and personal factors and components of the contextual factors and by using more neutral concepts. The ICF is intended as a tool for describing the degree of health, functioning and disability, which is to be used by policy makers, by health professionals, and by people to determine their own level of functioning.

The ICF framework

The conceptual framework of ICF is presented in Figure 2. The model distinguishes *Body functions and structure*, *Activities*, and *Participation.* Each of these outcomes may be affected by the health condition, but also by contextual factors, where the model distinguishes between *Environmental factors* and *Personal factors*. The processes depicted are bidirectional, meaning that all components influence each other, either directly or through other components.

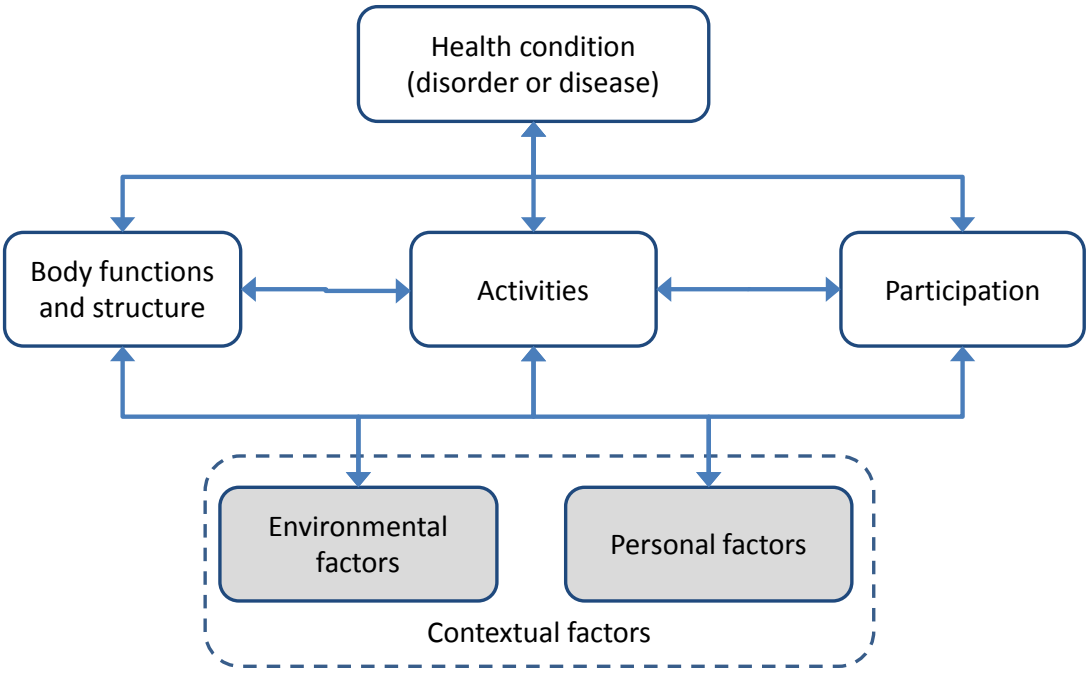

Figure 2. The International Classification of Functioning, Disability and Health (ICF)[22] model

The component *body functions and structure* consists of physiological functions of body systems including psychological functions, and body structures which describes function of the body at an anatomical level. This component is somewhat similar to the *impairment* component of the ICIDH model.

The component *activities* concern the execution of a task or action by an individual. The ICF uses the terminology of *activity limitations* when referring to difficulties an individual may have in executing tasks or actions. This component is somewhat similar to the *disability* component of the ICIDH model.

The component *participation* concerns involvement in a life situation. Thus, this component concerns an individual's performance in society. *Participation restrictions* are problems an individual may experience in involvement in life situations. This component is somewhat similar to the *handicap* component of the ICIDH model.

Coding of ICF

While the ICF offers a distinction between activities and participation in theory, the actual coding does not use the distinction, since activities and participation are coded together. For example, work is coded in section d on "Activities and Participation" in chapter 8 ("Major life areas") subsection d840-d859 ("Work and employment") (Figure 3)[22]. Here, performance at work could be coded under d8451 or under d8502 if the person is employed full time, otherwise under d8501 (see Figure 3 for definitions of each category).

For coding of activities and participation, two qualifiers are used. The *Performance qualifier* is used to describe the person's actual performance of a task or action in his or her current environment. This context includes environmental factors. The *Capacity qualifier* describes the person's ability to execute a task or an action in a hypothetical or real standard environment. The Capacity qualifier focuses on limitations that are inherent or intrinsic features of the individual. These limitations should be direct manifestations of the respondent's health state without assistance, such as help of another person, use of tools, or environmental qualifications.

Figure 3. Excerpts from the ICF coding system to illustrate coding of performance at work[22]

d ACTIVITIES AND PARTICIPATION

d8 CHAPTER 8 MAJOR LIFE AREAS

d840-d859 Work and employment (d840-d859)

d8451 Maintaining a job
Performing job-related tasks to keep an occupation, trade, profession or other form of employment, and obtaining promotion and other advancements in employment.

d8501 Part-time employment
Engaging in all aspects of work for payment on a part-time basis, as an employee, such as seeking employment and getting a job, doing the tasks required of the job, attending work on time as required, supervising other workers or being supervised, and performing required tasks alone or in groups.

d8502 Full-time employment
Engaging in all aspects of work for payment on a full-time basis, as an employee, such as seeking employment and getting a job, doing the required tasks of the job, attending work on time as required, supervising other workers or being supervised, and performing required tasks alone or in groups.

Both performance and capacity are coded using a 5 point scale:

0. **No difficulty**: the person has no problem
1. **Mild difficulty**: a problem that is present less than 25% of the time, with an intensity a person can tolerate and which happens rarely over the last 30 days.
2. **Moderate difficulty**: a problem that is present less than 50% of the time, with an intensity, which is interfering in the persons day to day life and which happens occasionally over the last 30 days.
3. **Severe difficulty**: a problem that is present more than 50% of the time, with an intensity, which is partially disrupting the persons day to day life and which happens frequently over the last 30 days.
4. **Complete difficulty**: a problem that is present more than 95% of the time, with an intensity, which is totally disrupting the persons day to day life and which happens every day over the last 30 days.

The contextual factors are factors describing the background of an individual's life or living, both personal and environmental. Personal factors include for example age, gender, lifestyle, education, ability to cope, socio-economic status or role expectations. Personal factors are not part of a health condition or health status and are not classified in ICF, but they may have an impact on the outcome. The environmental factors, which can either facilitate or worsen activities and participation, make up the physical, social and attitudinal environment in which people live and conduct their lives[22].

Discussions of the ICF

While the ICF has generated a lot of theoretical and research interest, it has also been criticized[25]. Much criticism has been focused on conceptual and methodological issues concerning the participation and environmental factors[25]. The ICF does not offer a clear operational distinction between activities and participation. Also, while the distinction between performance and capacity seems to work for description of activities, the usefulness of these qualifiers for description of participation seems doubtful. Participation concerns the fulfillment of social roles and social interaction and therefore must be described with respect to the actual situation (performance)[25].

From an occupational health perspective, the coding scheme for environmental factors appears to leave few opportunities for coding the work environment. The most relevant coding categories are shown in Figure 4.

e ENVIRONMENTAL FACTORS

e5 CHAPTER 5 SERVICES, SYSTEMS AND POLICIES

e590 Labour and employment services, systems and policies

e5900 Labour and employment services
Services and programs provided by local, regional or national governments, or private organizations to find suitable work for persons who are unemployed or looking for different work, or to support individuals already employed, such as services of employment search and preparation, reemployment, job placement, outplacement, vocational follow-up, occupational health and safety services, and work environment services (e.g. ergonomics, human resources and personnel management services, labour relations services, professional association services), including those who provide these services.

e5901 Labour and employment systems
Administrative control and monitoring mechanisms that govern the distribution of occupations and other forms of remunerative work in the economy, such as systems for implementing policies and standards for employment creation, employment security, designated and competitive employment, labour standards and law, and trade unions.

e5902 Labour and employment policies
Legislation, regulations and standards that govern the distribution of occupations and other forms of remunerative work in the economy, such as standards and policies for employment creation, employment security, designated and competitive employment, labour standards and law, and trade unions.

Figure 4. Excerpts from the ICF coding system to illustrate coding of the working environment[22]

Applying the ICF to Rheumatoid Arthritis

The coding framework of the ICF is so extensive that only a subset of categories would ever be used for any individual. Thus there has been interest to define core sets of categories that would be relevant for any particular disease. For rheumatoid arthritis, suggestions for a *comprehensive* and a *brief core set* has been published[26], using recommendations from 17 experts (see table 1). For the perspective of this PhD study, it is noteworthy that few experts endorse work and employment as an important code for inclusion, that the suggested category (d859) is not well defined in the ICF (no detailed definition is established) and that the work environment is not included at all in the suggestions for environmental factors.

Table 1. Categories included in the Brief ICF Core Set for rheumatoid arthritis[26]

ICF Component	Endorsed by %[1]	Code	Description
Body functions	100	b280	Sensation of pain
	100	b710	Mobility of joint functions
	85	b730	Muscle power functions
	70	b455	Exercise tolerance functions
	65	b780	Sensations related to muscles and movement functions
	15	b770	Gait pattern functions
	5	b134	Sleep functions
	5	b740	Muscle endurance functions
Body structures	100	s750	Structure of lower extremity
	100	s730	Structure of upper extremity
	85	s710	Structure of head and neck region
	70	s720	Structure of shoulder region
	15	s810	Structure of areas of skin
	10	s760	Structure of trunk
	5	s299	Eye, ear and related structures, unspecified
Activities and Parcitipation	90	d450	Walking
	90	d850	Remunerative employment
	75	d440	Fine hand use
	75	d410	Changing basic body position
	65	d445	Hand and arm use
	65	d230	Carrying out daily routine
	45	d430	Lifting and carrying objects
	40	d470	Using transportation
	30	d540	Dressing
	30	d510	Washing oneself
	30	d920	Recreation and leisure
	25	d770	Intimate relationships
	10	d859	Work and employment, other specified and unspecified
	5	d550	Eating
Environmental factors	92	e310	Immediate family
	92	e580	Health services, systems and policies
	69	e355	Health professionals
	69	e115	Products and technology for personal use in daily living
	62	e570	Social security services, systems and policies
	38	e155	Design, construction and building products and technology of buildings for private use
	23	e540	Transportation services, systems and policies
	23	e120	Products and technology for personal indoor and outdoor mobility and transportation
	15	e110	Products or substances for personal consumption
	8	e150	Design, construction and building products and technology of buildings for public use

[1] % of experts endorsing this code for inclusion in the brief core set

Table 2. ICF core set for disability evaluation in social security[27]

Chapter	Endorsed by %[1]	Code	Title
Mental functions	95	B164	Higher-level cognitive functions
Sensory functions and pain	65	B280	Sensation of pain
Functions of the cardiovascular, haematological, immunological and respiratory systems	45	B455	Exercise tolerance functions
Neuromusculoskeletal and movement-related functions	60	B710	Mobility of joint functions
	65	B730	Muscle power functions
Learning and applying knowledge	80	D110	Watching
	80	D115	Listening
	70	D155	Acquiring skills
	60	D177	Making decisions
General tasks and demands	100	D220	Undertaking multiple tasks
	100	D240	Handling stress and other psychological demands
Communication	85	D399	Communication, unspecified
Mobility	85	D410	Changing basic body position
	100	D415	Maintaining a body position
	95	D430	Lifting and carrying objects
	95	D440	Fine hand use
	95	D445	Hand and arm use
	70	D450	Walking
	100	D470	Using transportation
Interpersonal interactions and relationship	80	D720	Complex interpersonal interactions

[1] % of experts endorsing this code for inclusion in the brief core set (1st vote)

ICF core set for disability evaluation in social security

A core set for disability functioning has also been proposed[27]. It consists of 20 selected items from the ICF; five concerning body functions, and 15 concerning activities and participation. The core set is an attempt to represent an acceptable minimal set of items that is useful but not necessarily sufficient for the disability evaluation in the social systems of all participating European countries[27]. Compared to the core sets of chronic conditions, 20 categories is a low number, which was seen as an advantage that would increase the usefulness of the core set. Further, it was expected that the administrations in the various countries would wish to add categories according to national

standards and legislation. The expert group could not agree on any categories from the contextual constructs, so none were included. However, it was stated that work environment constitute an important and external element in the disability evaluation, and that when the core set is used, one must compare the level of functioning with work demands and work environment within the framework of the national social insurance legislation[27].

In conclusion, while the ICF provides a good overall framework for understanding what factors should be considered in analyzing the impact of RA on work, and when evaluating disability cases, the ICF do not include operational definitions and measurement strategies for work related outcomes such as sickness absence, unemployment, and disability pensioning. Thus, such operational definitions have to be developed outside the ICF. Interestingly, the core set for disability evaluation does not specifically refer to work. Also, the ICF place little emphasis on descriptions of the working environment. Thus, measurement of the working environment need to build on methods established in occupational health research.

The concept of work ability

The concept of work ability originated in studies of work among aging populations[28], but the concept is now used in a broader context. A literal interpretation of "work ability" would suggest that the concept refers to intra-individual skills. Thus Tengland suggest the following definition of general work ability:

> "A person has general work ability if he or she has the physical, mental and social health, standard basic competence, and basic occupational virtues that are required in order to perform some kind of work – work that most people (in the same age group and of the same sex) typically would be able to perform after a short period of training, given that the (physical, psycho-social and organizational) environment is acceptable, and if the person can stand the job."[29]

Using the capacity/performance distinction of the ICF, this can be understood as an attempt to define work ability as a capacity. However, given the complexities of modern work life, it is hard to see how work ability can be understood without any consideration as to what kind of work is to be performed. Ilmarinen, who has spearheaded the development of the work ability concept, emphasize that:

> "In occupational health, the work ability concept is built on the balance between a person's resources and work demands. A person's resources consist of health and functional abilities, education and competence, and values and attitudes. Work, on the other hand, covers the work environment and community, as well as the actual contents, demands, and organization of work."[28]

This is in line with the ICF concept of performance and with the component of participation as the fulfillment of roles in a social context. This PhD study will build on the interpretation of work ability outlined by Ilmarinen. This understanding of the concept is close to the concept of 'work functioning' that has been used in the literature to refer to how well a person functions while at work[30]. The word 'role' refers to the employment role or roles required in carrying out different tasks in everyday life – in line with the ICF component of participation. In practice, the assessment of work ability will partly build on self-report measures and partly on labor market consequences of reduced work ability: LTSA, unemployment and disability pension.

Labour market outcomes

LTSA works as a proxy for ill health. It can be seen as an early indicator of illness and has been proposed as a measure of physical, psychological and social functioning in studies of working populations[31]. LTSA is an important outcome for patients with RA, both from an individual and a societal perspective. For the individual patient, LTSA often leads to reduced income and loss of contact with colleagues[20]. Further, LTSA puts the patient at higher risk for permanent exclusion from the labor market[16;17]. From a societal perspective, LTSA represents a significant loss of production and is a substantial economic burden. LTSA is related to risk of unemployment, disability pension, and difficulties of returning to work from sickness and from unemployment[16-19].

Historically, RA patients have an increased risk of permanent loss of work ability, resulting in disability pension[16;32;33]. A decrease in the risk of disability pension during later years has been reported, but it is not known whether it merely reflected a reduction in disability pension in general, caused by political, demographic, and socioeconomic changes, or represented a disease-specific decline e.g. due to modern treatment strategies[15;34]. The same uncertainty applies to the risk of unemployment and the probability of return to work for patients with RA.

Work related outcomes in a national context

In order to understand the context of the transitions (shifts) between work, LTSA, unemployment and disability in this PhD study, the next paragraph gives a brief overview over the national context in which these transitions occur.

Denmark is a welfare state, with a relatively high labor market participation rate and relatively generous and accessible social benefits, but with a relatively low formal employment protection. In effect, Denmark has a high turnover of the work force between employments, but the work force experiences a high level of subjective job security. This unique combination of traits has been termed the flexicurity model. In Denmark, unlike most welfare states, neither the right to receive sickness absence benefits nor disability pensioning is based on membership of an insurance fund; both schemes are tax paid[35].

There is no consensus on the definition of LTSA. This may reflect cross-national differences in national sickness legislation. In this PhD project, LTSA was defined as the shortest length of consistently registered LTSA in DREAM for the duration of the particular study. For Cohort A, this was 3 weeks or more. For Cohort B, this was 4 weeks or more[36].

The right to receive disability pensioning was granted to Danish residents with limited work ability irrespective of a previous career on the labor market. A grant was given after a thorough - and often lengthy - case processing involving e.g. medical examination, and test of work ability[36].

Only the unemployment benefit scheme was linked to membership of an insurance fund; in the study period, around 80% of the work force was members of such unemployment insurance funds. A substantial part of the funds were however supported by the state; i.e. the tax payers. If members of these funds became unemployed and were available for the labor market, they could receive unemployment benefits. People with no membership of an insurance fund could receive social assistant benefit, but that did depend on a number of conditions including the amount of savings of the person and the income of a spouse, if any[36].

Unemployment is not a classic outcome in the RA literature; it appears in tables and figures with main focus on LTSA and/ or disability pension. RA patients are reported to experience fear of

losing their job due to arthritis and related functional outcomes[37]. Unemployment is hypothesised to be a consequence of RA, due to decreased work ability, but it is not well investigated. The Danish flexicurity model makes it on the one hand easy for companies to hire diseased people; on the other hand, there is little protection against being fired for employees with a disease. Specifically, employers were not responsible for paying for LTSA episodes, and they could without economic costs dismiss people being on sick leave due to the low employment protection[38].

The physical working environment

Physical working conditions differ from one job to another. The physical demands of the job considers the movements, actions and body positions that the employee performs during working hours, which in most cases is necessary for the employee to perform the work[39]. They are closely related to the work process, and depend on the various arrangements of the work premises. It is essential to keep a safe, healthy and comfortable environment as it contributes to work efficiency and the well-being of workers[40]. Many jobs and work tasks involve, however, some degree of physical work demand, which has been shown to have consequences for the workers. For instance, a high work load measured as working with arms lifted above shoulder level, lifting or movement of loads, working with the neck or back bent or twisted, and/or frequent repetition of forceful movements (e.g. cleaners and workers in slaughterhouses) have all been associated with an increased risk of development of musculoskeletal disorders or unspecific musculoskeletal disorders and complaints in one or more body parts[41-45]. Some kinds of physical work demands increase the risk of sickness absence and early retirement, and this association differs between sexes, age groups and industries[3;46;47]. The analyses in this PhD consider the physical working environment, as RA affects the body functioning, and it is hypothesized that the RA patients may be more sensitive to factors in the physical working environment than the general population. In Cohort A, physical job exposure was measured by the use of a job exposure matrix[48;49], which were able to stratify the populations based on D-ISCO codes in Statistics Denmark into physical exposure groups, to be included in the analyses. In Cohort B, the physical job exposure was a self-reported measure consisting of 10 items from the Danish Work Environment Cohort Study (DWECS)[3], divided into physical demands at work and exposure to cold and draught (see table 3 for details).

Psychosocial working environment

Empirical evidence points to the associations between psychosocial work factors and health related outcomes[50]. Factors in the psychosocial working environment may be risk factors for health

outcomes, such as cardiovascular disease[51], musculoskeletal disorders[52], stress[20;47;53-56] and mental disorders[57;58]. Others are considered protective factors that enable employees to achieve their goals, deal with high work demands and stimulate personal development[59;60].

The dimensions used in Cohort B stems from the Copenhagen Psycho-Social Questionnaire (COPSOQ)[55]. The COPSOQ is a comprehensive instrument, that not only measures specifically defined health-hazardous constellations at work as other questionnaires do, but has the objective of assessing all relevant aspects of the psychosocial work environment[55]. In this PhD study concerning RA patients and work related outcomes, the aim was to investigate which psychosocial work environment factors predict LTSA in patients with RA, by choosing the dimensions from COPSOQ, that seemed to be most relevant for this specific population and the research aims stated[55]. The dimensions were Influence at work, Emotional demands, Degrees of freedom, support from supervisor, Quality of leadership, and Corporate social responsibility. (Table 3 presents the wording of the questions used).

Table 3. Wording of questions on physical function and the working environment

Physical function	
Does your health now limit you in:	*vigorous activities*[1] *moderate activities*[1] *lifting or carrying groceries*[1] *climbing several flights of stairs*[1] *climbing one flight of stairs*[1] *bending kneeling or stooping*[1] *walking more than a mile*[1] *walking several block*[1] *walking one block*[1] *bathing or dressing*[1]
Physical demands at work	
How much of your time at work are you…	*standing in the same spot,*[2] *working with arms lifted* [2] *bending or twisting in the back or neck* [2] *doing repetitive movements* [2] *kneeling* [2] *squatting* [2] *pushing*[2] *pulling*[2]
Exposure to cold or draught	
How much of your time at work are you…	*Subjected to the cold(Work outside in the winter, in chilly rooms, e.c.t.)*[2] *Subjected to a draft (air current)?*[2]
Influence at work	
Do you have a large degree of influence concerning your work?[3]	
Can you influence the amount of work assigned to you?[3]	
Do you have any influence on what you do at work? [3]	
Do you have a say in choosing who you work with? [3]	
Do you have any influence on your work schedule? [3]	
Emotional demands	
Do you have to relate to other people's personal problems as part of your work? [3]	
Degrees of freedom	
Can you decide when to take a break? [3]	
Can you leave your work to have a chat with a colleague? [3]	
If you have some private business, is it possible for you to leave your place of work for half an hour without special permission? [3]	
Support from supervisor	
How often is your nearest superior willing to listen to your problems at work?[4]	
How often do you get help and support from your nearest superior? [4]	
How often does your nearest superior talk with you about how well you carry out your work? [4]	
Quality of leadership	
To what extent would you say that your immediate superior:	*makes sure that the individual member of staff has good development opportunities?*[5] *gives high priority to job satisfaction?* [5] *is good at work planning?,* [5]
To what extent does the management	*communicate a clear and positive vision for the future?* [5] *encourage the employees to view the problems in a new way?* [5] *clearly express their values and live by them?* [5]
Corporate social responsibility	
Is there space for employees with various illnesses or disabilities?[6]	

From paper III

[1]Response categories: *"Yes, limited a lot, Yes, limited a little, No, not at all"*.

[2]Response categories: *Almost all the time, Approximately 3/4 of the time, Approximately 1/2 of the time,*

Table 3. Wording of questions on physical function and the working environment

Approximately 1/4 of the time, Rarely/very little, Never".
[3]Response categories: *"Always, Often, Sometimes, Rarely, Never/Almost never"*.
[4]Response categories: *"Always, Often, Sometimes, Rarely, Never/Almost never, Not relevant"*.
[5]Response categories: *"To a very high degree, To a high degree, To some degree, To a slight degree, To a very slight degree, Not relevant"*.
[6]Response categories: *"To a very high degree, To a high degree, To some degree, To a slight degree, To a very slight degree"*.

Patients and methods

This PhD study is based on two different cohorts of RA patients, Cohort A, used in the analyses in study A, and Cohort B, that is used in study B.

Data sources

The following registers were used; The Danish Rheumatologic Database (DANBIO), The Danish Register of the Evaluation of Marginalization (DREAM), the National Patient Register (NPR), and Danish National Prescription Registry (PRESCRIBE). DANBIO is a nationwide registry that provides data on the disease course of adult patients with inflammatory rheumatic joint diseases[61-63]. The NPR includes all hospital admissions (since 1977) and outpatient activities (since 1995) in Denmark, and patients are registered by diagnoses according to the International Classification of Diseases codes (1978-1993: ICD-8; 1994-2011: ICD-10)[64]. The NPR was also used to identify co-morbidity, in combination with the Danish National Prescription Registry (PRESCRIBE), which provides information on all prescribed medications dispensed from Danish pharmacies since 1995.

We retrieved individual data on LTSA, unemployment, and disability pension from the DREAM register, which provides weekly information on social transfer payments for all residents in Denmark (since July 1991). It is based on data from the Danish ministries of Employment, Social Affairs, and Education, and has been shown to be suitable for follow-up of social consequences of disease[65]. To be eligible for sickness absence benefit the employee must have worked minimum 120 hours during the previous 13 weeks[66].

Data from these registers were linked through the central personal register (CPR) number, a unique personal identifier given at birth to all Danes.

Cohort A

From DANBIO, we identified a cohort of RA patients aged 18-59 years at the time of RA diagnosis and who got the disease between 1994 and 2011, N = 4865. For each patient, 10 controls from the general population were identified in the nationwide registers of Statistics Denmark, matched on gender, age and city size. To identify additional RA patients that were not registered in DANBIO, the control group was screened in the NPR for individuals who had been hospitalized or received outpatient treatment with an RA diagnosis three or more times, since this has been shown to be a valid approach to identify RA patients in the LPR[67]. Thus, the following ICD-8 codes were used: 712.19 (Syndroma Felty), 712.39 (Arthritis rheumatoides alia et non specificata), 712.59 (Fibrositis rheumatoides chronica nodularis), and the following codes from ICD-10 were used: DM05

(Arthritis rheumatoides seropositiva), DM06 (Arthritis rheumatoides alia) except DM06.1 (Still's disease)[67]. Such patients (N=1,812) were included in the RA group and excluded from the control group (Total number of RA patients = 6,677). Individuals with uncertain RA status (i.e. only one or two relevant RA diagnoses in the NPR) were excluded from the analysis. The controls were then re-matched to the merged population, by gender, age and city size, leading to 8-10 controls per patient. The study period of Cohort A started on January 1st 1994 and follow up ended on April 1st 2011.

Cohort B

A total of 5,124 patients with RA aged 18-64 years at 25th of March 2011 were identified in the DANBIO registry (see Figure 5). The patient population was merged with the DREAM database, and patients on early retirement, on disability pension, not resident in Denmark, on welfare, patients who had died or patients who registered as not willing to participate in research via their cpr number were excluded. The population was limited to patients aged 18-59 years at May 1st 2010. The final RA population to receive questionnaire consisted of 2,013 patients. The questionnaire was sent on May 3rd 2011, by offering the possibility to receive a health and working environment profile based on their personal answers in the questionnaire. The thought was to motivate the respondents to answer the questionnaire. In case of non-response, reminders were sent after 2 and 4 weeks. After 5 weeks, Statistics Denmark contacted all non-responders by phone. A total of 1,735 (87%) RA patients answered the questionnaire, of which 1,728 could also be found in the registers in Statistics Denmark. The following respondents were excluded: RA patients who had been working when included in the analysis, but who was on LTSA (n = 120) or disability pension (n = 428) at the time of answering the questionnaire. Persons working on special terms, or receiving early retirement pension were all classified as receiving disability pension and excluded (N=428). Patients who were students, emigrants, or on leave during the entire 2 year follow up period (n = 8) were also excluded, as were those who had missing values on one or more items relevant for the analyses in this study (n=277). Thus, the final cohort B comprised 895 working patients with RA aged 18-59 years. A general population comparison sample - matched on gender and age - was identified in Statistics Denmark (1:10) to form a comparison group for distribution on background variables. Patients were followed up in DREAM and follow-up ended at June 30th 2013.

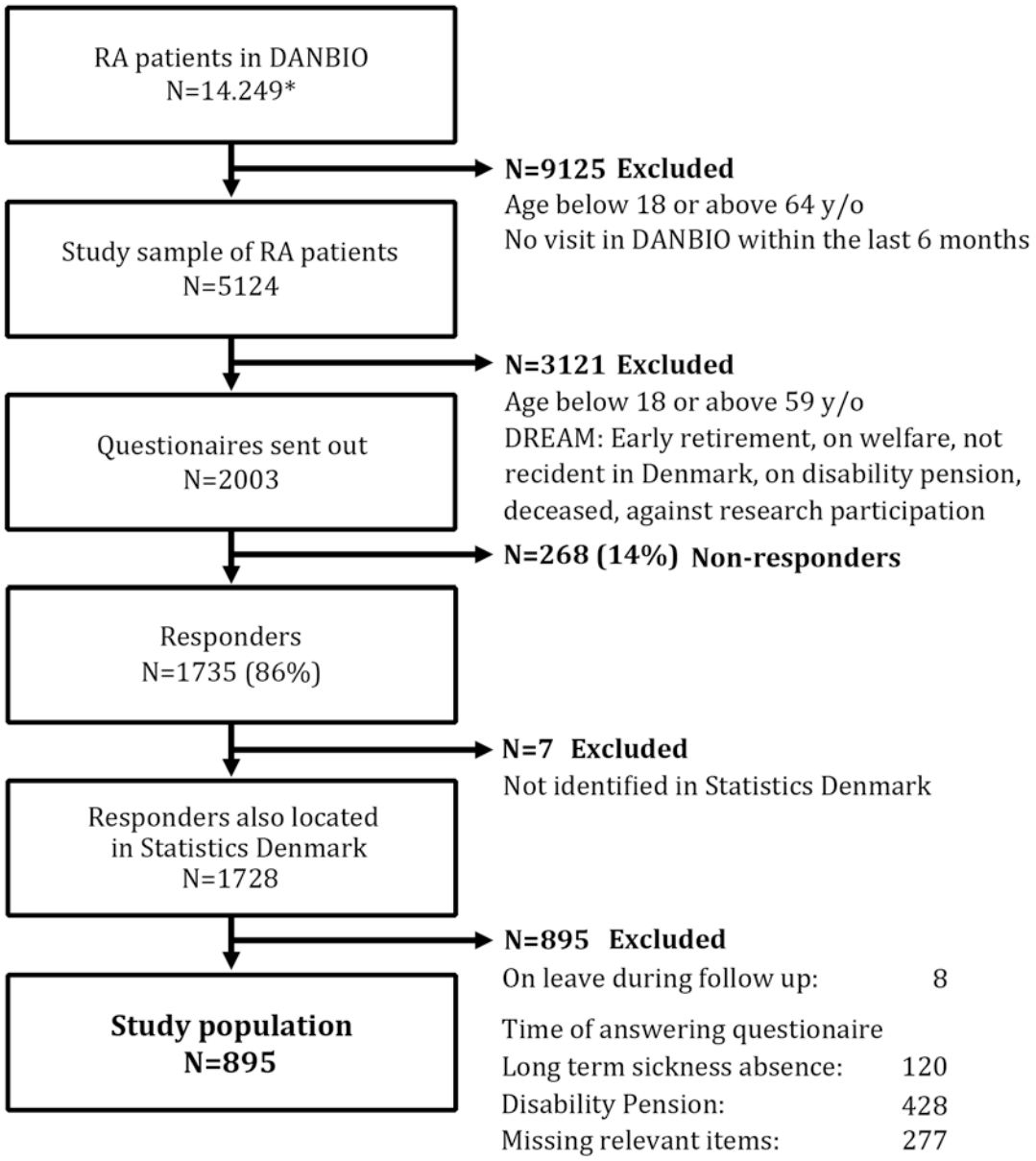

Figure 5, Patient disposition over inclusion and exclusion criteria defining the study population of RA patients in study 3/cohort B. *By 31st of December 2013[68]

Outcomes - Definitions

LTSA

Individuals were classified as being on LTSA if receiving sickness absence benefits for a period of at least 3 weeks for cohort A and at least 4 weeks for cohort B. This definition was used because,

the sickness absence became registered in DREAM after 3 or more weeks of sickness absence, at which time point the municipalities became responsible for managing the sickness absence cases[69;70]. Follow up started January 1st 1994 and ended April 1st 2011 for cohort A, and follow up started May 3rd 2011, when the questionnaires were sent, and ended two years later in Cohort B.

Unemployment

The Danish model contains two types of unemployment schemes: insurance-based and income-based. To receive compensation under the insurance-based unemployment scheme, the unemployed person must have been a member of the insurance scheme for at least one year, the unemployed person must register as unemployed on the first day without a job, and the unemployed person must have been employed for at least 52 weeks during the last 3 years before unemployment. The income-based unemployment scheme administered by the municipalities and compensation can be achieved if the unemployed person is not insured or if the insurance period has expired (4 years between 1998 and 2010, then 2 years). The size of the compensation is dependent on various factors; it is calculated on the basis of the household income, it depends on the unemployed persons age (below or above 25), civil status, and if any children must be provided for[71].

Disability pension

A disability pension is a social benefit for people with permanent loss of work ability, which makes providing for oneself impossible. Attempts to increase the persons work ability must have been tried without success. The disability pension is permanent, and the compensation period lasts until retirement age[71]. Persons working on special terms, such as flexible job or receiving early retirement pension, were also classified as receiving disability pension.

Work

Persons who were not registered as receiving any benefits (including house wives) were classified as working.

Covariates

The following five variables were included in the analyses of data in both cohort A and B: 1. Gender (male, female), 2. Ethnicity (immigrant, immigrant descendent, or Danish); 3. Household composition (Single or cohabitants with or without children, including singles living with children); 4. City size (capital centre, closest suburbs, the metropolitan area, city > 100,000 inhabitants, city 10,000 – 100,000 inhabitants, or the rest of the country); 5. Highest obtained education (Elementary school/High school, Vocational training, Tertiery/Polytecnic school, Higher education (e.g. Master,

PhD)). In addition, we controlled for seasonal changes in variation in LTSA. All variables except gender and immigrant status were treated as time-dependent variables, thus taking into account that individuals may change status during the period of observation.

Additional covariates in Cohort A

Seven variables were included in analyses of Cohort A, in study 1 and 2: 1. Rheumatoid arthritis classified as sero-negative (including non-specific RA), or sero-positive; 2. Gender (male, female), 3. Age (18-29, 30-39, 40-49, or 50-59 years), 4. Calendar year (1994-1999, 2000-2005, or 2006-2011); 5. Physical job exposure (total lifts of 0 kg/day, 1-5999 kg/day, > 6000 kg/day); 6. Somatic co-morbidities and 7. psychiatric co-morbidities.

Physical job exposure was estimated from job type (retrieved from DREAM) using a job exposure matrix based on the Danish version of the International Standard of Classification of Occupations (DISCO-88[64;72]). The job exposure matrix is described elsewhere[48;49]. For the present study, physical job exposure was categorized into three groups according to estimated kilograms lifted per work day: 0 kg/day, 1-5999 kg/day, > 6000 kg/day.

To control for diseases that could be competing causes of LTSA, we adjusted for 18 groups of chronic, somatic comorbidities (cancer, thyroid diseases, diabetes, other endocrine, nutritional and metabolic diseases, obesity, neurological diseases, chronic diseases of the ears, hypertension, chronic pulmonary diseases including asthma, cardiac disease, stroke, inflammatory bowel disease, diseases of the liver, diseases of the skin, kidney diseases, gynecological diseases, and transplantations) and 4 groups of psychiatric comorbidities (dementia, substance abuse, anxiety, and depression).

Additional covariates in Cohort B

Information on age, and job type was identified via the central population register (CPR register) at Statistics Denmark. Age was defined as age in years at the time of response to the survey. Job type was classified via the Danish version of the International Standard of Classification of Occupations[73] (DISCO-08).

Development of the Work and Health – RA Questionnaire

The questionnaire was developed to measure self-reported health and physical function, self-reported work ability, and the self-reported physical and psychosocial working environment. It

consisted of scales and items from already well established surveys (The Danish National Working Environment Cross-sectional Study(DANES)[74], The Short Form -36 Standard in Danish (SF-36)[75], Karolinska Sleep Questionnaire (KSQ)[76], Arthritis Self-Efficacy Scale (ASES)[77], Danish Work Environment Cohort Study (DWECS)[3], The Copenhagen Psychosocial Questionnaire (COPSOQ)[55]), supplemented with a few new questions to address work-specific arrangements due to RA, and a modified version of the Standford Scale for RA patients.

Table 4. Items and domains in the Work and health – RA Questionnaire

Domain	Number of items	Tested in interviews	Source
Date	1	8	DANES[a]
Feedback to respondents	1	8	DANES[a]
Physical function (PF)	10	9	SF-36[b]
Role Physical (RP)	4	9	SF-36[b]
Bodily Pain (BP)	2	9	SF-36[b]
General Health perceptions (GH)	5	9	SF-36[b]
Vitality (VT)	4	9	SF-36[b]
Social Function (SF)	1	9	SF-36[b]
Role Emotional (RE)	3	9	SF-36[b]
Mental Health (MH)	5	9	SF-36[b]
Sleep	4	12	KSQ[c]
Self-efficacy	8	9	ASES-8[d]
Sociodemographic variables	6	16	DANES[a]
Smoking	2	16	DWECS[e]
Exercise	1	16	DANBIO[f]
Your employment	13	14	DWECS[e]
Your primary Workplace	7	14	DWECS[d]/COPSOQ[g]
Special arrangements at the workplace due to RA	12	8	Developed to this questionnaire
Physical work environment	13	10	DWECS[e]
Self-rated work ability	5	10	DWECS[e]
Psychical work environemtn	26	9	COPSOQ[g]
The overall impression of the workplace	9	9	COPSOQ[g]
Comments	1		
Questions, total	138		

*[a]The Danish National Working Environment Cross-sectional Study(DANES), [b]The Short Form -36 Standard in Danish(SF-36), [c]Karolinska Sleep Questionnaire (KSQ), [d]Arthritis Self-Efficacy Scale, [e]Danish Work Environment Cohort Study (*DWECS), [f]*From the patient part of the standard survey used during visits at the rheumatologist clinic, [g]The Copenhagen Psychosocial Questionnaire (COPSOQ)*

The SF-36 Health Survey

SF-36 is a generic health survey[75], which means that it is not linked to certain diseases, but is relevant for all individuals. SF-36 covers general health and functioning. Some of the items cover physical functioning; others cover mental health while others again reflect both physical and psychic health. Characteristic for SF-36 is that it covers positive health aspects. This is similar to the health perception of WHO in the ICF[78], and has the advantage that it is more specific in most populations than instruments focusing only on negative health consequences of disease. SF-36 is fit to be combined with other instruments specific to the project at hand. SF-36 is well documented[75].

The Copenhagen Psychosocial Questionnaire

The Copenhagen Psychosocial Questionnaire (COPSOQ)[55] is a tool developed at NRCWE in Denmark with the aim of assessing and improving the psychosocial work environment. It was originally developed in 1997, and it consists of three instruments: A long questionnaire for research use, a medium size questionnaire to be used by work environment professionals, and a short version to be used by the workplaces. This questionnaire concept has now become the national Danish standard for assessing psychosocial work environment, and both the short and middle length questionnaires are widely used by workplaces and work environment professionals. In 2004-5 the second version of COPSOQ was developed, on the basis of the first COPSOQ. COPSOQ II also had three versions, and was developed in a study of the psychical working environment of Danish employees, from a representative sample of 3188 employees[79].

When using COPSOQ II in research, the researcher chooses the questions relevant for the specific research question, and mixes them, to prevent respondent from using a stereotyped response pattern[55].

In study B, items from both COPSOQ I and II were used. The dimension degree of freedom was included from COPSOQ I, because we expected it to be a protective factor of LTSA for RA patients.

Karolinska Sleep Questionnaire (KSQ)

The sleep quality scale from Karolinska was included[76]. The four items had high internal reliability and they loaded on the same factor in the analyses conducted by Pejtersen et al[80] when developing COPSOQ II. Further, KSQ has worked well in other studies[81;82].

Danish Work Environment Cohort Study Questionnaire

The Danish Work Environment Cohort Study (DWECS)[3] is a large, nationwide open cohort study by the National Research Centre for the Working Environment (NRCWE) to systematically map the

working conditions, health and lifestyle of Danish employees. The DWECS was conducted in 1990, 1995, 2000, 2005, and 2010, before a major change in sampling and the questionnaire. We used items from the 2010 questionnaire.

The Danish National Working Environment Cross-sectional Study Questionnaire

The purpose of the Danish National Working Environment Cross-sectional Study(DANES)[74], was to complement the knowledge obtained from DWECS. In September 2008, the researchers behind DANES sent questionnaires to 20,600 people. We used items on sociodemographic factors from the DANES questionnaire. The idea to use an offer on personal feedback as an incentive was also taken from the DANES study.

Standford Arthritis Self-Efficacy Scale (ASES)

The Standford Arthritis Self-Efficacy Scale (ASES)[77] exists in the original 20 item (ASES-20) version and a shorter 8 item version (ASES-8), that replaced the longer version, as the short form is much less burdensome for subjects, as is stated on the web-site for Standford Patients Education Research Center. The ASES was developed in USA to measure perceived self-efficacy to cope with the consequences of RA and to understand change processes relating to patient education programs and rehabilitation outcomes, and was based on the 1981 Conference on Outcome Measures, with further items being developed following focus groups interviews with patients[77]. We have translated the ASES-8 into Danish, to include in my Health and Work –RA questionnaire.

Work and Health - RA

As we wanted to ask employed RA patients if they had special arrangements at work, we phrased 12 questions (items) that addressed this subject and tested them in interviews with patients. The first items consider if there are arrangements considering the employment that maintains the employer employed (e.g. flexjob or $56 where the municipalities pay for sickness absence from the first day instead after 3 weeks). The 5 items focus on the work tasks and if the RA patient has had special training or education as a consequence of RA, if the patient has had new tasks or if the patient has changed job because of RA. Five items consider help at the workplace e.g. personal assistance, special tools, or other kinds of RA related arrangements at work. Room was left for the patients to specify special arrangements as a consequence of RA.

Order of items in the Work and Health – RA questionnaire

The Work and Health – RA questionnaire was structured with the general health and functioning questions first. Thus, if it was sent to someone who was not employed, due to delayed registering in DREAM, they were able to answer these questions anyway.

Test of the Health and Work –RA Questionnaire in Interviews

When we had the first version of the questionnaire ready, it was tested by interviewing RA patients right after they had answered the questions. The interview aimed to test if the questionnaire covered all relevant items for RA patients. The composition of the questionnaire was evaluated and changed during the interview process, until it had the best structure. Other aims of the interview process were to investigate how RA patients perceived their illness, coping strategies related to having RA at the workplace, and to identify processes that could lead to reduced work ability and labour market exclusion. The interviews were conducted at the rheumatologist clinic at Glostrup Hospital, when RA patients came to their regular visit. 22 patients were asked, 21 accepted. The respondents were 14 females and 7 males, and from various social classes. Most of the respondents were employed and between 18 and 64 years of age, one male of 74 were interviewed about self-efficacy, and one unemployed female were interviewed about the first half of the questionnaire. The interviews were recorded for later analysis.

Ethics

The study was approved by The Danish Data Protection Agency, journal number: 2015-41-3828.

Statistical Analyses

Cox Proportional Hazards model applied to grouped survival data

Cox Proportional Hazards model is a commonly used regression technique for dealing with data of the "time-to-event" type. It is useful to describe the effect of several covariates on life time, or in a study period, between two individuals or two groups. The measure of effect is a Hazard Ratio (HR), which is an expression of relative risk (hazard) of an event between two groups e.g. RA patients and controls. The relative risk is dependent on the assumption that it remains proportionally constant between the groups or individuals at all times. The analyses are called survival analyses, although the event need not be deaths, but can be LTSA and other work related outcomes, as in this PhD study[83;84].

The relative risk of work related outcomes was estimated using the Cox Proportional Hazards model (SAS 9.2 PROC PHREG) with latent entry. In Cohort A, the patient was included in the analysis when he or she was diagnosed with RA, and the matched controls appeared at the same time, while in Cohort B, the patient entered when answering the questionnaire. LTSA was treated as a repeated event by the use of a frailty model[83;85], and the assumption of proportionality was investigated by visual inspection of cumulative hazard curves for each covariate.

Study A

In study A, my analyses of LTSA assumed separate risks in; 1) the first year after diagnosis, 2) the subsequent years after diagnosis. Subjects were censored if they died, turned 60 years, emigrated, became unemployed, received disability pension or at the end of the observation period (April 1st 2011), whichever came first. Subjects were temporarily out of risk if they were on maternity leave, other kinds of leave, or students. Initial analyses were performed separately for the two genders, but since the results were similar, the final analysis was performed on the combined population, controlling for gender. We analyzed the risk of LTSA for sero-negative and sero-positive RA patients and found no difference. Thus, the two groups were combined in the final analyses for study A.

Using Cohort A, we analyzed the relative risk of the RA population and the general population in three models of increasing complexity. In model 1, analyses were controlled for sociodemographic confounders (age, gender, ethnicity, urbanization, highest obtained education, physical job exposure and family type). In model 2, we also controlled for somatic and psychiatric comorbidities. In model 3, interactions between rheumatoid arthritis and all the covariates were added as well, one at a time. Each analysis of interaction between RA and another covariate was controlled for the ten covariates. The study was corrected for multiple testing, i.e. for random events that could falsely appear significant in the analyses with the multi-state models, by using the Benjamini Hochberg correction[86].

Multi-state models

The shifts between being at work, on LTSA, unemployed, and receiving disability pension was analyzed. Figure 6 illustrates the possible shifts in work status on the labour market.

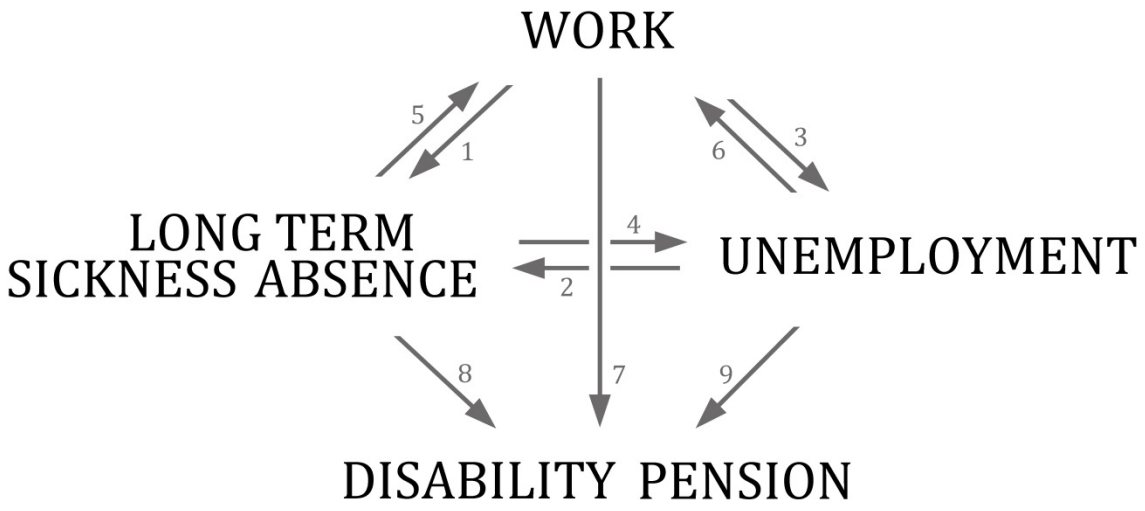

Figure 6. The possible shifts in the work related states used in the multistate model[85]
(From Paper II)

We refer to the shifts as *transitions* (arrows at Figure 1, #1 to #9), and to the work-related outcomes as *states*. In the model, the participants can leave and reenter the states work, LTSA, and unemployment throughout the study period, so these states were treated as transient states. When a person received disability pension, he or she was not at risk for further transitions, so the state disability pension was treated as an absorbing state[85;87]. If a person moved to other kinds of work-related states (e.g. maternity leave or studying), he or she was temporarily out of risk. Subjects were censored if they died, turned 60 years of age, emigrated, or reached the end of the observation period, whichever came first. Based on person years (PY) and the number of events, we calculated the rates of the different transitions (events/1000 PY).

Initial analyses evaluated the number of PY in each state, the number of transitions to other states, and the rate for each transition. In the multivariate analyses, the relative risks for each transition were estimated separately by calculation of HR using the Cox Proportional Hazards model, controlled for all covariates. Then, we analyzed the HR of the transitions, stratified by the three calendar time periods (1994-1999, 2000-2005, 2006-2011), still controlling for all covariates.

We present HR with 95% confidence intervals, and we corrected the results from the multi-state model for multiple testing using the Benjamini Hochberg correction[86]. SAS version 9.2 was used

for statistical analyses.

Study B

Using Cohort B, we analyzed the HR for LTSA in a two year period (2011-2013) for RA patients at work. The effect of the self-reported factors from the questionnaire on LTSA was analyzed using the Cox Proportional Hazards model for repeated events with a random person effect (frailty model)[83;85]. The underlying time variable was time since answering the questionnaire (Figure 2). Patients entered the analysis when answering the questionnaire (late entry) and were followed until LTSA, censoring, or temporarily out of risk. Subjects were censored if they died, turned 60 years, or received disability pension before the end of the observation period (i.e. two years after study entry). Subjects were temporarily out of risk if they were on maternity leave or other kinds of leave, if they emigrated or became students. Subjects who became unemployed during follow up were kept in the analysis, since LTSA is also registered for the unemployed. Each work environment variable was included as an independent variable in the "crude" analyses (without control for covariates) and in adjusted analyses (controlled for covariates and physical functioning). All covariates except gender and immigrant status were treated as time-dependent variables, thus taking into account that individuals may change status during the period of observation.

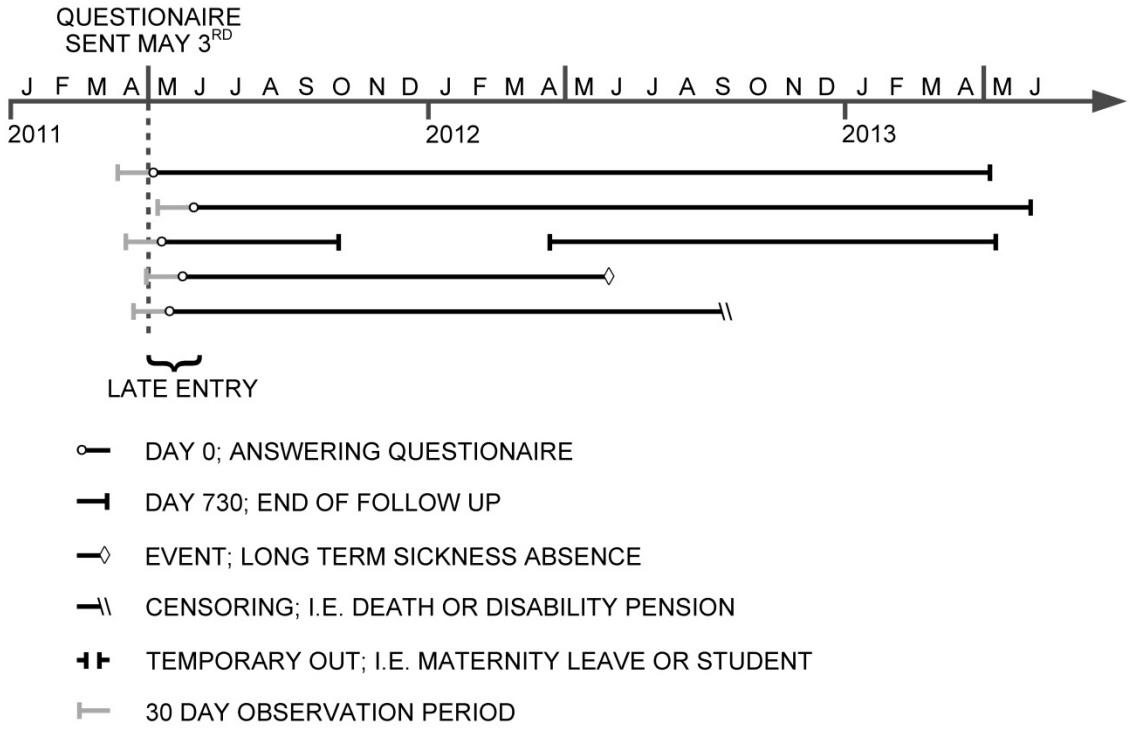

Figure 7. Cox proportional hazards model with late entry. At day 0 the questionnaire was answered and the RA patient entered the analysis. Thus day 0 depended on the answering date, and so did end of follow up, which was 2 years after answering (day 730). If an RA patient had LTSA (the event), or was censored, the patient was out of risk and left the analysis. If the RA patient was on leave or became a student, the RA patient was temporary out of risk, and entered the analysis again when they returned to work or unemployment afterwards (frailty model). (From Paper III)

Results

Characteristics of cohort A and B

In cohort A, 74% were female, and 74% were 40-59 years of age (table 5). Age, gender, household status, level of education, physical job exposure and city size were largely similar between patients and controls, whereas more patients than controls were of Danish origin. Thirty-one percent of the RA patients had one or more somatic comorbidity, and 9% had one or more psychiatric comorbidity. Compared to the controls, more patients suffered from somatic, but not psychiatric, comorbidities.

In cohort B, 74% were female, and 83% were 40-59 years of age. More RA patients were ethnic Danes, living in a relationship, had tertiary education or higher, and worked as knowledge workers. Small percentages of RA patients had been on LTSA or received unemployment benefits within the 30 days prior to answering the questionnaire (and had returned to work since being at work was a condition for participating in cohort B).

Table 5. Characteristics of the RA populations and the matched controls

		Cohort A (papers I+II)		Cohort B (paper III)	
		RA Patients (n=6,677)	General Population (n=56,955)	RA Patients (n=895)	General Population (n=8950)
Co variates		%	%	%	%
Year of diagnosis	1994 - 1999	38.5	-	-	-
	2000 - 2005	31.9	-	-	-
	2005 - 2011	29.6	-	-	-
Gender	Female	73.6	73.3	74.4	74.4
	Male	26.4	26.7	25.6	25.6
Age	≤ 29 years	7.5	7.2	3.0	2.6
	30-39 years	18.7	19.7	14.5	13.1
	40-49 years	33.1	33.8	32.9	30.0
	50-59 years	40.8	39.3	49.6	54.4
Ethnicity	Danish	94.6	87.0	94.4	84.2
	Immigrant	5.2	12.8	3.6	13.1
	Descendants	0.3	0.2	-	-
	Not available	-	-	0	2.7
Household composition/ Family type	Couples[a]	77.4	77.3	80.0	75.3
	Singles	22.6	22.7	20.0	22.0
	Not available	-	-	0	2.7
City size	Capital centre	14.1	12.6	-	-
	Closest suburbs	13.9	15.5	-	-
	The metropolitan area	6.5	7.6	-	-
	City > 100,000	9.9	12.1	-	-
	City 10,000 – 100,000	29.4	27.5	-	-
	The rest of the country	26.2	24.8	-	-
Highest obtained education	At most high school	33.7	33.2	16.1	23.3
	Vocational training	39.6	35.8	41.7	36.4
	Tertiary/polytechnic school[b]	20.9	22.2	31.5	26.6
	Higher education (e.g. Master, PhD)	4.2	5.9	9.7	8.6
	NA	1.6	2.9	1.0	5.1
Job type	Management	-	-	3.9	3.0
	Knowledge workers I [c]	-	-	27.4	20.2
	Knowledge workers II [d]	-	-	16.2	10.6
	Clerical support work	-	-	9.4	8.05
	Sales, service and care	-	-	13.5	13.7
	Work with high physical load[e]	-	-	10.3	14.3
	Not available	-	-	19.3	30.3

Table 5. Characteristics of the RA populations and the matched controls

		Cohort A (papers I+II)		Cohort B (paper III)	
		RA Patients (n=6,677)	General Population (n=56,955)	RA Patients (n=895)	General Population (n=8950)
Co variates		%	%	%	%
Physical job exposure Estimated kg lifted per day	0	43.3	44.5	-	-
	1-5999	31.5	32.3	-	-
	≥ 6000	25.2	23.2	-	-
Somatic Comorbidity	0	69.4	75.7	-	-
	≥1	30.6	24.3	-	-
Psychiatric Comorbidity	0	91.3	92.2	-	-
	≥1	8.7	7.8	-	-
LTSA in the previus 30 days	No	-	-	99.2	-
	Yes	-	-	0.8	-
Unemployment in the previous 30 days	No	-	-	96.7	-
	Yes	-	-	3.4	-

[a]Cohort A: Cohabitants with or without children, and singles living with children, Cohort B, no information on children
[b] Prepares people for specific trades, crafts and careers at various levels from a trade, a craft, technician, or a high professional practitioner position in careers such as engineering, accountancy, nursing, medicine, architecture, law etc.
[c] Science, engineering, medical science, education, economy, law (e.g. professors, lawyers, engineers)
[d] Technicians and associate professionals in transport and aviation, health care, in trade, finance, administration, law, sports, religion
[e] Military, farming, gardener, forestry, hunting, fishing, craft, machine operator, drivers, construction workers, routine manual work

Relative risk of LTSA compared to the general population (Specific aim 1)

Out of 2735 person years (PY) of observation for RA patients who were in the first year after diagnosis, 983 events (start of LTSA) were observed (rate= 0.36 events/PY). In RA patients who were observed during subsequent years after diagnosis, 2951 events were observed during 19,577 PY (rate= 0.15 events/PY). For controls, 2417 events were observed within the first year of diagnosis of the index patient (out of 30,399 PY, rate= 0.08 events/PY). In subsequent years, 21,404 events were observed during 266,270 PY for a similar rate of 0.08 events/PY.

Table 6 summarized the final model (Model 3) from analyses by proportional hazards models of the relative risk of LTSA compared to the general population (Paper I). RA patients had substantially higher risk of LTSA, especially in the first year after diagnosis (HR= 5.4), and in subsequent years (HR= 2. 4).

Table 6. Results on Relative Risk of Long Term Sickness Absence Proportional hazards model

	During the first year after diagnosis		More than one year after diagnosis	
Variable	HR	(95% CI)	HR	(95% CI)
Rheumatoid arthritis[a]				
No	1		1	
Yes	5.4***	(4.2-6.8)	2.4***	(2.1-2.8)
Calendar year				
1994-1999	1		1	
2000-2005	1.7***	(1.5-1.9)	2.0***	(1.9-2.1)
2006-2011	1.7***	(1.5-2.0)	2.0***	(1.8-2.1)
Gender				
Female	1		1	
Male	0.7***	(0.6-0.7)	0.7***	(0.7-0.8)
Highest obtained education				
Elementary school/high school	1		1	
Vocational training	1	(0.9-1.0)	0.9***	(0.9-1.0)
Tertiary/polytechnic school	0.8***	(0.7-0.9)	0.8***	(0.8-0.9)
Higher education (e.g. Master, PhD)	0.4***	(0.3-0.5)	0.5***	(0.5-0.6)
NA	1.2	(1.0-1.6)	1	(0.9-1.1)
Physical job exposure (kg/day)				
0	1		1	
1-5999	1.6***	(1.5-1.8)	1.3***	(1.3-1.4)
≥ 6000	1.9***	(1.7-2.1)	1.5***	(1.5-1.6)
Somatic comorbidity[b]				
No	1		1	
Yes	1.6***	(1.5-1.8)	1.5***	(1.5-1.6)
Psychiatric comorbidity				
No	1		1	
Yes	2.2***	(2.0-2.5)	1.9***	(1.8-2.0)
Rheumatoid arthritis x calendar year				
1994-1999	1		1	
2000-2005	1	(0.8-1.2)	0.9	(0.8-1.1)
2006-2011	0.9	(0.7-1.1)	0.8***	(0.7-0.9)
Rheumatoid arthritis x gender				
Female	1		1	
Male	1.1	(0.9-1.3)	1.1*	(1.0-1.3)

Table 6. Results on Relative Risk of Long Term Sickness Absence Proportional hazards model

	During the first year after diagnosis		More than one year after diagnosis	
Variable	HR	(95% CI)	HR	(95% CI)
Rheumatoid arthritis x somatic comorbidity[b]				
No	1		1	
Yes	0.7**	(0.6-0.9)	0.8***	(0.7-0.9)
Rheumatoid arthritis x psychiatric comorbidity				
No	1		1	
Yes	0.6***	(0.4-0.7)	0.8**	(0.7-0.9)

From Paper I, Tables 2 and 3 – Model 3.
All analyses were controlled for ethnicity, urbanization, season, and family type
[a] Patients with RA (N=6,677) and matched controls (N=56,955)
[b] Somatic morbidity except rheumatoid arthritis
* < 0.05 ** <0.01 *** < 0.001

Changes in the risk of LTSA over time (Specific aim 2)

For the general population, the relative risk of LTSA was higher in the years 2000-2005 and 2006-2011, compared to the years 1994-1999 (HR=1.7/2.0). The risk of LTSA also increased for RA patients, but the increase was smaller than for the general population – as indicated by interaction parameters smaller than 1 for the RA * calender year interaction term. Comparing the years 2006-2011 to 1994-1999 the hazard ratio for the general population was 2.0, but the hazard ratio was 1.8 for RA patients diagnosed more than a year ago (Paper I, Table 4). Thus, the excess risk of LTSA in patients with established RA was reduced by 20% in the years 2006-2011 compared to 1994-1999. For RA patients in the first years after diagnosis, the RA * calender year interaction terms were not significantly different from 1.

Impact of other risk factors on LTSA (Specific aim 3)

For both the general population and for RA patients, the relative risk of LTSA was lower for persons with high education but higher for persons holding jobs with heavy physical exposure (table 6). In the general population, relative risk of LTSA was lower for men, but higher for persons with somatic or psychiatric comorbidity. The same trends were seen among RA patients, but the ratios were smaller, as evidenced by the interaction terms (table 6). These trends were seen both in the first year after diagnosis and in the subsequent years. The latter results will be used for illustration. In the general population, the HR for men was 0.7, while the HR for male RA patients as compared to female RA patients was0.8 (Paper I, Table 4). In the general population sample, the

HR for persons with somatic morbidity (other than RA) was 1.5, while RA patients with somatic comorbidity had an HR of 1.2 compared to RA patients without somatic comorbidity. Finally, in the general population sample, the HR for persons with psychiatric morbidity was 1.9, while RA patients with psychiatric comorbidity had an HR of 1.5 compared to RA patients without psychiatric comorbidity (Paper I, Table 4). For any combination of risk factors for LTSA, an RA diagnosis constituted a considerable additional risk factor both in the first year after diagnosis and in subsequent years (Paper I, Table 5).

Chance of return to work and risks of unemployment and disability pension (Specific aim 4)

Table 7 (from Paper II, Table 3) shows the hazard rations of 9 transitions. Results stem from multi-state analyses by proportional hazards models, controlled for gender, age group, size of resident city, year of diagnosis, season of year, immigrant status, household composition, highest obtained education, physical job exposure, somatic and psychiatric co-morbidities (but without interaction effects). Thus, the HR for sickness absence for RA patients in the first year after diagnosis (HR=4.0) is the same as the one estimated in paper I (Model 2). This HR is lower than the estimate when interaction terms are included in the model (HR=5.4, Table 6). The risk of LTSA is also higher for unemployed RA patients than for unemployed persons from the general population HR = 1.62/2.46 (Table 7, Transition #2). The probability of returning to work from either LTSA or from unemployment was lower for RA patients than for the general population, and this was particularly pronounced for RA patients in the first year after diagnosis HR=0.60/0.77 (Table 7, transitions #5 and #6).

In the first year after diagnosis, the risk of unemployment was similar in RA patients and in controls (Table 7, transition #3). In subsequent years, the risk of unemployment was lower for the RA patients. For RA patients on LTSA, the risk of unemployment was lower than for persons on LTSA in the general population (Table 7, transition #4). From work, LTSA, and unemployment, the risk of disability pension was significantly higher for RA patients in the first year after diagnosis with further increases in the subsequent years (Table 7, transitions #7, #8, and #9).

Table 7. Hazards ratios for 9 transitions. Rheumatoid arthritis patients compared to matched general population controls. Proportional hazards models

		Disease duration < 1 y			Disease duration ≥ 1 y		
#	Transitions	HR		(CI95%)	HR		(CI95%)
1	Work – Sickness absence	4.00	***	(3.64-4.30)	1.84	***	(1.75-1.94)
2	Unemployment – Sickness absence	2.46	***	(1.99-3.04)	1.62	***	(1.45-1.81)
3	Work – Unemployment	0.92		(0.83-1.03)	0.82	***	(0.77-0.87)
4	Sickness absence – Unemployment	0.42	***	(0.35-0.51)	0.62	***	(0.56-0.69)
5	Sickness absence – Work	0.60	***	(0.55-0.66)	0.78	***	(0.75-0.82)
6	Unemployment – Work	0.77	***	(0.70-0.85)	0.80	***	(0.76-0.83)
7	Work – Disability pension	8.60	***	(6.34-11.67)	12.20	***	(10.96-13.58)
8	Sickness absence – Disability pension	1.52	***	(1.26-1.84)	2.75	***	(2.54-2.98)
9	Unemployment – Disability pension	2.36	***	(1.57-3.54)	3.41	***	(2.92-3.98)

From Paper II
All analyses controlled for gender, age group, size of resident city, year of diagnosis, season of year, immigrant status, household composition, highest obtained education, physical job exposure, somatic and psychiatric co-morbidities
* P < 0.5, ** P < 0.01, *** P < 0.001, corrected for multiple testing

Changes over time in chance of return to work and risks of unemployment and disability pension (Specific aim 5)

Table 8 (from Paper II Table 4) presents results comparing HR for 9 transitions according to 3 time periods. As discussed above, the excess risk for LTSA for RA patients decreased from the years 1994-1999 to 2005-2011 (Table 8, Transitions #1 and #2). No significant changes over time were seen in the HR for unemployment (Transitions #3 and #4) or for the HR for return to work (Transitions #5 and #6). For disability pension, a trend towards lower hazard ratios was seen for all comparisons and the decrease was statistically significant for the transition from work to disability pension in the first year after diagnosis (Transition #7). The risk of disability pension in the subsequent years after diagnosis did not change significantly. The risk of disability pension after LTSA decreased significantly over time in patients with more than 1 year's disease duration (Transition #8). The same trend was seen in patients with disease duration less than one year, but the trend did not reach statistical significance when correcting for multiple testing.

Finally, the relative risk for RA patients to transition from unemployment to disability pension (Transition #9) also seemed to decrease, but the results were not statistically significant.

Table 8. Hazard ratios for 9 transitions for RA patients in different time periods

	Disease length < 1 y			Disease length ≥ 1 y		
	HR	(95% CL)	P[a]	HR	(95% CL)	P[a]
Work to Sickness absence (#1)			0.085			0.000*
1994 – 1999	4.69	(3.82-5.76)		2.25	(1.99-2.54)	
2000 – 2005	4.08	(3.56-4.67)		1.99	(1.85-2.14)	
2006 – 2011	3.63	(3.2-4.11)		1.63	(1.51-1.75)	
Unemployment to Sickness absence (#2)			0.035			0.004*
1994 – 1999	3.03	(2.03-4.52)		2.13	(1.72-2.64)	
2000 – 2005	3.06	(2.19-4.26)		1.78	(1.51-2.11)	
2006 – 2011	1.69	(1.17-2.44)		1.24	(1.03-1.49)	
Work to Unemployment (#3)			0.776			0.669
1994 – 1999	0.95	(0.79-1.16)		0.83	(0.75-0.91)	
2000 – 2005	0.93	(0.78-1.11)		0.79	(0.72-0.87)	
2006 – 2011	0.87	(0.71-1.07)		0.83	(0.76-0.91)	
Sickness absence to Unemployment (#4)			0.311			0.705
1994 – 1999	0.34	(0.21-0.55)		0.68	(0.54-0.85)	
2000 – 2005	0.49	(0.37-0.66)		0.59	(0.5-0.69)	
2006 – 2011	0.39	(0.29-0.53)		0.62	(0.54-0.72)	
Sickness absence to Work (#5)			0.764			0.664
1994 – 1999	0.65	(0.51-0.82)		0.80	(0.7-0.91)	
2000 – 2005	0.61	(0.53-0.71)		0.80	(0.75-0.86)	
2006 – 2011	0.58	(0.52-0.66)		0.77	(0.73-0.81)	
Unemployment to Work (#6)			0.044			0.249
1994 – 1999	0.83	(0.70-0.98)		0.82	(0.75-0.89)	
2000 – 2005	0.86	(0.74-0.99)		0.76	(0.71-0.82)	
2006 – 2011	0.65	(0.55-0.78)		0.81	(0.76-0.86)	
Work to Disability pension (#7)			0.002*			0.186
1994 – 1999	15.17	(9.65-23.86)		12.32	(10.36-14.64)	
2000 – 2005	5.28	(3.18-8.76)		13.31	(11.22-15.8)	
2006 – 2011	4.83	(2.11-11.05)		10.29	(8.22-12.88)	
Sickness absence to Disability pension (#8)			0.007			0.004*
1994 – 1999	2.14	(1.36-3.35)		3.49	(2.83-4.32)	
2000 – 2005	1.88	(1.40-2.51)		2.97	(2.64-3.35)	
2006 – 2011	1.08	(0.80-1.45)		2.40	(2.15-2.69)	
Unemployment to Disability pension (#9)			0.495			0.009
1994 – 1999	2.82	(1.13-7.03)		4.18	(2.84-6.14)	
2000 – 2005	3.03	(1.52-6.01)		4.24	(3.37-5.33)	
2006 – 2011	1.86	(1.02-3.38)		2.74	(2.20-3.41)	

From paper II.

[a] Test of equal hazard rates across the 3 time period

*Significant when corrected for multiple testing

Individual and work related risk factors for LTSA (Specific aim 6)

Table 9 (from Paper III, table 4) presents results for the association of each work environment variable and LTSA in unadjusted and adjusted analyses (controlling for ethnicity, job type, previous LTSA and physical function). The risk of LTSA was significantly increased for RA patients with high physical job demands and was significantly lower for patients having high degrees of freedom at work and for patients working under a leadership they rated positively. The latter two associations were weakened slightly when controlling for covariates, but remained significant at a 5% level. No significant associations were found for working in a cold environment, for working jobs with high emotional demands, for having influence at work, for social support from supervisors, nor for working in companies with high corporate social responsibility.

Table 9. Hazard ratios of long term sickness absence according to working environment variables with and without control for covariates. Rheumatoid arthritis patients (n= 895)

	Bivariate associasions			Controlled associations*		
Working environment variables	HR	95% CL	P	HR	95% CL	P
Physical exposure at work	**4.31**	**(1.34-13.91)**	**0.01**	**4.94**	**(1.36-18.00)**	**0.02**
Cold working environment	1.65	(0.87-2.40)	0.18	1.41	(0.65-3.05)	0.39
Emotional demands at work	1.45	(0.79-3.46)	0.16	1.32	(0.78-2.22)	0.30
Influence at work	0.63	(0.33-1.19)	0.15	0.58	(0.30-1.15)	0.12
Degrees of freedom at work	**0.41**	**(0.22-0.78)**	**0.01**	**0.52**	**(0.27 -0.98)**	**0.04**
Social support from supervisors	0.57	(0.29-1.15)	0.12	0.67	(0.33-1.38)	0.28
Quality of leadership	**0.39**	**(0.18-0.85)**	**0.02**	**0.43**	**(0.20-0.95)**	**0.04**
Social responsibility at work	0.51	(0.26-1.01)	0.05	0.61	(0.29-1.27)	0.19

From Paper III

*Controlled for ethnicity, job type, physical functioning, and previous long term sickness absence

Discussion

The first part of the discussion reviews the conceptual framework for the PhD project. In the second part, the main results of the PhD project are discussed. The third part of the discussion reviews the strengths and weaknesses of the methods used in the project. A further discussion of the study results can be found in papers I-III.

Conceptual framework

This PhD study used the ICF as a conceptual framework to identify and classify factors to include in the analyses. Within the ICF, the description of the impact of a disease on the individual's situation includes the interplay between body functions and structures, activities, and participation as well as contextual factors such as environmental and personal factors[88]. So with the ICF, the current understanding of the burden of the RA disease comprises not only clinical symptoms, but also other aspects that have an impact on living with RA. Earlier measures of functioning in RA patients typically cover only selected aspects of the whole patient experience associated with RA, and the measures vary quite considerably regarding the concepts included[26].

Figure 8 illustrates how the ICF model was applied in this study.

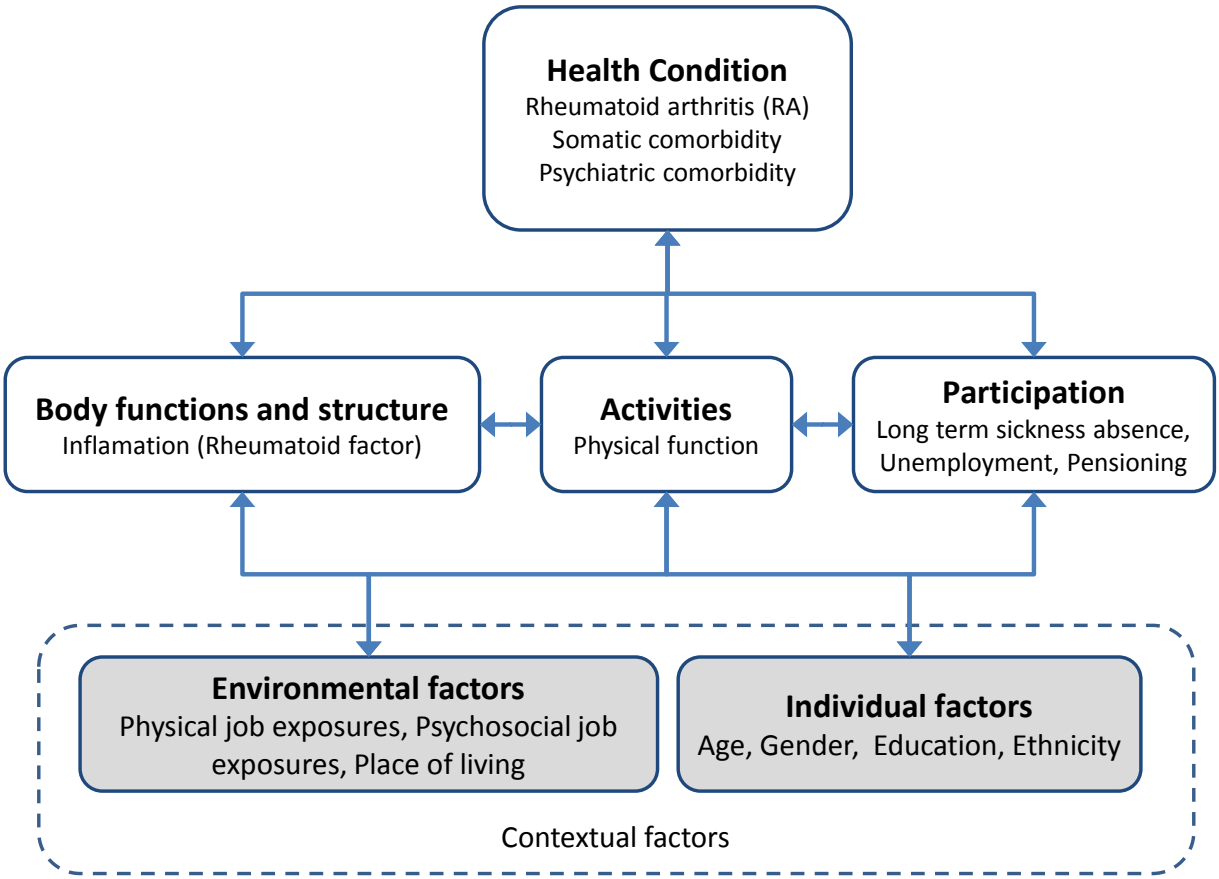

Figure 8. The ICF model as applied to the PhD study

Health condition

Besides RA, which is the focus of this PhD study, somatic and psychiatric comorbidities are also included in the register analyses for paper I and II. The list of the somatic comorbidity index did not include diseases such as ischemic heart disease, chronic infections, and osteoporosis that are known to occur more frequently among RA patients, possibly due to shared aetiology[89-91]. Thus, controlling for these diseases could lead to underestimation of the effect of RA.

Body functions and structure

The inflammatory processes of RA give rise to symptoms such a fatigue and pain, swollen joints with limited movement and subsequently loss of cartilage, bone erosions, and joint deformity[1;91]. A classical risk factor for more severe disease is the presence of rheumatoid factor (seropositive RA)[8]. In the register analyses for paper I and II, patients with seropositive RA were identified based on the

hypothesis that they would be at higher risk for LTSA and disability pension. In cohort B, data on self-reported pain and fatigue were recorded. However, in the final analyses, we decided to include only physical function which is a strong predictor of LTSA[75].

Activities

No data on *activities,* the execution of a task or action, was available for cohort A. In cohort B, limitations in activities were assessed by self-report of the individual's physical functioning[75].

Participation

This PhD study focus on one aspect of participation: the ability to work. Limitations in work ability were explored through registration of LTSA, unemployment, and disability pension. Also, improvement in work ability was assessed by return to work from LTSA or unemployment. While LTSA and disability pension is strongly dependent on an individual's health, unemployment may be unrelated to an individual's health condition. An individual may become unemployed by ending a time limited position, or as an effect of economic priorities at the company. However, due to the Danish flexicurity system, person with a chronic health condition may become unemployed and a chronic health problem may affect the change of finding a new job[92]. For these reasons, we wanted to estimate the risk of unemployment and the return to work rate for RA patients.

Environmental factors

The environmental factors in the ICF framework are described as factors that may influence body structure and function, activity, or participation[22]. Work ability depends on the employed person but also on the working environment[28]. The assessment of the working environment differed between the two cohorts. In cohort A, physical job exposure was measured through a job exposure matrix[48;49], where the exposure was measured as amounts of kilograms lifted per day, based on job type. In cohort B, the working environment was assessed by self-report. The *physical working environment* as assessed through questions concerning body postures and repetitive movements as well as questions on exposure to cold or draught[3]. The *psychosocial working environment* was assessed through questions on influence degrees of freedom at work, emotional demands, support from supervisor, quality of leadership, and corporate social responsibility[55]. Additional environmental factors included were household composition and city size.

Personal factors

We included the personal factors age, gender, education, and ethnicity in the analyses, based on previous research that had showed that they had effect on the risk of LTSA and disability pension[2;93-95].

Main results

The relative risk of LTSA for RA patients compared to the general population (Specific aim 1)

Patients with RA are at high risk of long term sickness absence[16-19]. We found that RA increased the risk of LTSA approximately five times during the first year after diagnosis and twice during subsequent years compared to the general population (paper I). This is in line with other studies, that showed a dramatic increase in mean days of long term sickness absence in the time right after diagnosis[16;33]. We extended these findings even further by showing that this applied both to patients who were at work and patients who were unemployed prior to the long term sickness absence. The large hazard ratio of LTSA for RA patients was robust even after controlling for a large number of covariates, indicating that there is substantial room for further improvement in the handling of recent-onset RA.

Changes in the relative risk of LTSA over time (Specific aim 2)

Compared to 1994-1999, the excess long-term risk in patients with more established disease (which was defined as more than one year since diagnosis) decreased by approximately 20 % in 2006-2011. Thus, in the years 2006-2011, a woman with RA had a HR of 4.8 for LTSA in the first year after diagnosis, and a hazard ratio of 1.9 in subsequent years. In comparison, in 1994-1999 the HRs were 5.4 and 2.4, respectively. These results are in line with previous studies[16;33], but the large size of this study, the comparison cohort from the general population and nationwide registers with very high data completeness allowed us to perform more precise estimations of the relative risks and more detailed analyses of potentially modifiable factors. These results suggest that modern treatment strategies including, but not limited to[96;97], the use of biologics, reduce LTSA for RA patients. We did not have access to information on treatment, so a direct association between treatment and reduced risk was beyond the analyses. Other factors may also have influenced the risk of LTSA, e.g. improved treatment strategies also for conventional drugs, earlier diagnosis, and advances on health education programs. Previous studies have shown positive results of treatment with biological drugs on LTSA. In a cohort study comparing RA patients starting biological treatment with the general population, a decrease of almost 30% in LTSA was observed during the first year of biological treatment[18]. The study only included RA patients who completed the biological

treatment, which may have biased the result. Also, a decrease in LTSA as a result of treatment with biologics was shown in two RCT studies[98;99]. In the first study, the odds for favorable employment status was ≈1.5 in patients treated with combination treatment (adalimumab + methotrexate (MTX)) versus MTX alone[98]. In the second study, combination treatment (certolizumab pegol plus MTX) led to a cumulative annual gain of ≈ 40 full work days and ≈30 fewer days with reduced productivity compared to placebo plus MTX[99].

The positive trends described above concern the excess risk of LTSA compared to the general population within the same period. For both patients and the general population, the risk of LTSA increased from 1994-1999 to 2000-2005 probably due to changing conditions in the Danish labour market (with a possible additional effect of improved registration)[100]. The risk remained high for the general population during 2006-2011, but decreased for RA patients – in particularly those with more established disease.

Impact of other risk factors (e.g. physical work demands, age, gender, education, comorbidities) on LTSA (Specific aim 3)

Similar to the general population, patients with RA with short education and/or high physical strain at work had an increased risk of LTSA. This is an important finding, since level of education and physical job strain are potentially modifiable factors. The results are in accordance with results from other studies on risk factors for LTSA in general population samples[101]. In both genders, low social class was a risk factor for LTSA. Further, physical working environment factors explained more of this risk than health behavior. Studies of RA patients have found higher risk of LTSA in patients with short education[102] but few quantitative studies of RA patients have included measures of the physical job exposures in relation to LTSA.

Generally, females have higher risk of LTSA[103], and this was also the case in this study, where females had a higher risk of LTSA than males. However, the difference between male and female RA patients was smaller than in the general population.

We had expected higher risk of LTSA for patients with sero-positive RA, but this was not the case. A review including 4 studies of sero-positive RA and work disability found positive association between RF and disability in two studies and no association in two other studies[20].

The role of comorbidities has rarely been investigated in the context of disability pension in RA research. A Finnish study on psychiatric and cardiovascular comorbidities as causes of disability pension in patients with recent-onset RA found that the 9-year cumulative incidence of disability pensions caused by psychiatric or cardiovascular comorbidities was only 11% or 4%, respectively, of that caused by RA itself. Compared to the general population, the risk of work disability due to CV disease was increased[90]. The study focused on co-morbidities known to be associated with RA, whereas our co-morbidity variable was defined as comorbidity besides the ones associated with RA, as it would be difficult to estimate the impact of RA and comorbidities when RA could be a cause of the comorbidity. As the modern treatment strategies reduce the risk of LTSA and disability pension caused by RA, the relative role of comorbidities may increase[90]. In this PhD study, patients with RA and somatic or psychiatric comorbidity had a higher risk for LTSA than patients without, but the combined risk was less than the product of the two risk ratios.

Chance of return to work and risks of unemployment and disability pension (Specific aim 4)

In addition to the increased risk of LTSA discussed previously, the study found reduced probability of return to work and higher risk of disability pension. As stated earlier, the most common way to achieve disability pension is from sickness absence[102]. After a peak in sickness absence 1 year after diagnosis, a decline was shown in a Swedish study, which showed that the decline in sickness absence was almost fully offset by an increase in disability pension[16]. This was in accordance with our results from the multistate model, which showed that the most common trajectory to disability pension was from long term sickness absence, for both RA patients and controls, and the relative risk for RA patients was high. While fewer persons shifted from work to disability pension, the relative risk for RA patients was even higher, and the risk was also markedly increased for unemployed patients (paper II).

The chance of returning to work from sickness absence was markedly reduced for RA patients relative to sick-listed controls from the general population, especially in the first year after diagnosis. However, it should be noted that the DREAM register does not distinguish between a sick-listed employee and a sick-listed unemployed person until the sick-listed person reports him or herself unemployed. It is possible that losing a job prolongs the sickness absence period and delays return to work[85].

However, the chance of returning to work from unemployment was also significantly lower compared to unemployed controls, both in the first year after diagnosis and in the subsequent years. To our knowledge, this outcome has not been investigated before in an RA population.

In a Swedish study, the average number of unemployment days among all RA patients was lower than for the general population[16]. Our results using multi-state models provide more detailed knowledge of unemployment for RA patients: The risk of becoming unemployed is lower for RA patients compared to the general population, but if unemployed the RA patient has a lower chance of returning to work (Paper II). However, as discussed below, the low risk of unemployment may, at least in part, be explained by registration bias.

For newly diagnosed RA patients in a Swedish RA cohort, the most important predictor of future sick leave and disability pension (measured together), was work ability the month before RA diagnosis[102]. This is in line with our results that physical function is a strong predictor of LTSA. The Swedish study also found that unemployment predicted more days with reduced work ability defined as days on sick leave or disability pension compared to working RA patients[102]. In paper III, unemployment in the month before entering the study was not a risk factor for LTSA.

Changes over time in chance of return to work and risks of unemployment and disability pension (Specific aim 5)

In addition to the changes in risk of LTSA discussed previously, results showed reductions from 1994 to 2011 in the risk of disability pension compared to the general population. These risk reductions were significant concerning the transition from work to disability pension in newly diagnosed patients (<1 year since diagnosis) and concerning the transition from sickness absence to disability pension in patients with more established disease (≥1 year since diagnosis). One may speculate that these risk reductions in part can be attributed to altered treatment strategies, e.g. early and aggressive use of csDMARD and bDMARD. It has been shown in large randomized clinical trials that bDMARD combination therapy has dramatically improved the treatment of RA[104-106]. In a longitudinal observational study of RA patients receiving bDMARDs[107], the treated patients showed increased work ability over a 5 year period. The increase in self assessed work ability was parallel to decreased disease activity and improvement in physical functioning and pain[107].

Despite the good results from the bDMARDs, it has been reported that the goal of achieving a good response according to the European League Against Rheumatism (EULAR) criteria (good EULAR response)[108], or even remission was not met in 60-80% of the RA patients treated with a bDMARD[62;109]. Results from DANBIO showed that most RA patients are treated with csDMARDs, and that over the period from 2006 to 2013, an increasing fraction of these patients fulfil the treatment goal set up by EULAR (see Smolen 2010[110]), although the goal has not yet been achieved in a substantial proportion of patients in routine care[54]. Since the relative risk of disability pension remains much higher than in the background population (paper II), there is an unmet need of initiatives that may help to retain patients with RA in the working force.

While the risk of disability pension in RA patients with established disease remains at least 2.5 times higher than for the general population (paper II) the risk has diminished considerably compared to the years 1994-1999. It is tempting to ascribe this risk reduction to the improvements in treatment, but the change may also reflect changes in political and economic conditions, age structure, increased educational level and less physically demanding jobs[15].

Individual and work related risk factors for long term sickness absence (self-reported health, work ability, psychosocial and physical working environment factors) (Specific aim 6)

In light of the increased risk of LTSA and disability pension discussed above, it is important to identify potential risk factors at the workplace, which might be modified. Only limited research has been done in this field within RA. A previous cross-sectional, quantitative study of 210 employees found an increased risk of sick leave for patients with low control over their job[54]. Also, passive coping behaviour was associated with increased sick leave, as were indicators for disease severity such a pain and reduced physical function[54]. Studies using qualitative interviews found that suitable working conditions, influence and especially support and positive attitudes from leader and from colleagues were important for maintaining the workability of RA patients[111;112].

Paper III addressed physical and psychosocial work environment risk factors for LTSA in a large population of RA patients using a prospective design. A strongly increased risk of LTSA was found for patients with high physical job demands and a reduced risk for RA patients with high degrees of freedom at work and high ratings of quality of leadership. These effects were robust even after controlling for covariates with significant association with LTSA among RA patients: previous LTSA, physical functioning, ethnicity and job type. Thus, while the results are generally in

agreement with the few previous studies of RA patients, some nuances are added. Thus, while physical demands at work were a strong risk factor, emotional demands was not a significant risk factor for LTSA. Also, degrees of freedom – such as flexibility in taking breaks – seemed more important than influence over work in general. Finally, quality of leadership seemed more important than experienced social support. It may be speculated that in quantitative studies social support is best assessed as the *opportunity for social support* (for which quality of leadership may be seen as a proxy) rather than *experienced social support*, because the latter is invariably confounded with the need for support.

To a large extent, our results also concur with results for the general population. The association between physical job demands and LTSA is well established[47]. Also, studies have found that "poor quality of leadership" increased the risk of LTSA for female employees[58]. However, LTSA risk factors for men in the general population were "high emotional demands" and demands for "hiding emotions"[58]. Such results were not found in this study of patients with RA.

Strenghts and weaknesses of the research methods

Identification of RA patients

The use of the nationwide DANBIO database for identification of patients with RA is a strength of the study. However, *as discussed in paper I and II*, the patient group may be influenced by selection bias: DANBIO was started in year 2000; i.e. RA patients between 18 and 59 years old, who died between 1994 and 1999, were not registered in DANBIO and only included in the study if identified from the NPR controls. Since such patients would be expected to have serious illness, the risk estimate for LTSA for the period 1994-1999 and the reduction in HR from 1994-1999 to 2006-2011 may be underestimated. In cohort B, where RA patients where included only if they were employed, further selection is highly likely to have occurred, since RA patients on LTSA or disability pension were excluded. This may have led to underestimation of the hazard ratios for the risk factors studied in cohort B.

Use of general population controls

The use of a control group matched on age, gender and residence area provided a sound basis for estimating the impact of RA on the risk of LTSA, unemployment and for disability pension in cohort A. In cohort B, the purpose of the general population group was the assessment of the degree of selection that had taken place within the RA group. Thus, baseline questionnaire data was not

collected from the control group, nor was the group followed up with regards to LTSA, unemployment and disability pension.

The DREAM register

Use of the DREAM register has many advantages: within the limitations posed by the definition of LTSA, registration is highly complete and does not depend on self-report. However, since DREAM did not collect data on sick leave shorter than 3 (or 4) weeks, total sick leave cannot be calculated. Also, absence of any social payment is used as a proxy for being employed. This will cause misclassification of persons who are unemployed but supported by their spouse and thus not receiving any social benefits. Due to the relatively fine masked Danish welfare system, this group is small (in particular for a patient group like RA) but it does exist[71]. It should also be noted that the group classified as receiving disability pension includes persons working on special conditions. This is in line with previous studies[69;85], but the proportion of persons working on special conditions may be higher for the RA groups than for other groups.

Measurement of physical job exposure

Physical job exposure was assessed differently in the two cohorts. In cohort A, physical exposure was assessed through a job exposure matrix[48] using job codes to estimate total kg lifted per day. A job exposure matrix allows physical job strain to be assessed in large population studies without having to rely on person self-report. However, the method also has obvious disadvantages: since a particular job code may cover jobs with very different requirements, misclassification is unavoidable. Also, the available job exposure matrix is not directed for the physical strains that may be particularly relevant for RA patients, such as requirements for gripping and fine movements of the hands. In cohort B, physical job exposure was assessed through self-report. This allowed for a more detailed assessment, but has other disadvantages, such as the risk of report bias. In conclusion, the two different assessment methods have different advantages and disadvantages. The fact that LTSA was predicted regardless of methods lends more credibility to the result.

Measurement of psychosocial job exposure

Physical job exposure was assessed by self-report in cohort B. While a risk of self-report bias is unavoidable, we used standard questions that have undergone tests of validity and reliability[55;57] and been successfully used in previous studies[53;57;79]. The selection of domains of psychosocial job exposure to be included in this study was based on the literature[3;53;58;113] and on results from qualitative interviews during pretesting of the questionnaire. However, it is possible that not all

relevant domains have been included. Thus it is possible that standard measures according to the demand-control model[114;115] or the effort-reward imbalance[56;116] model may be useful within the RA context.

Conclusion

With respect to the specific aims, the following conclusions can be made:

In patients with RA, diagnosed between years 1994-2011 (Cohort A):

1. The relative risk of LTSA for patients with RA was approximately five times higher during the first year after diagnosis and twice as high during the subsequent years compared to the general population. Increased risk of LTSA was found for both unemployed RA patients and patients who were working prior to the LTSA.
2. Compared to the period 1994-1999, this excess high risk of LTSA for RA patients in the following years after diagnosis decreased by approximately 20 % in 2005-2011.
3. For both RA patients and the general population, short education and/or high physical job strain were risk factors for LTSA. Sero-positive RA patients had the same risk of LTSA as the sero-negative RA patients, thus the biomarker RF was not a significant risk factor. RA patients with somatic or psychiatric co-morbidities had increased risk of LTSA compared to RA patients without, but the "impact" of co-morbidity in terms of relative risk was lower than in the general population.
4. The chance of returning to work from LTSA or unemployment was markedly reduced for RA patients relative to general population controls on LTSA or unemployment, especially in the first year after diagnosis. The risk of unemployment for RA patients was similar to or lower than for the general population both in early and more established disease. The relative risks of disability pension were higher for RA patients compared to the general population controls.
5. The relative risk of LTSA and disability pension for RA patients compared to the general population was lower in 2005-2011 than in 1994-1999. The chance of returning to work for RA patients did not change in the follow up period.

In patients with RA who were working in 2011 and followed up for two years (Cohort B):

6. The risks of LTSA was significantly increased for RA patients with high physical job demands and significantly lower for patients having high degrees of freedom at work and for patients working under a leadership they rated highly. Non-significant associations were found for working in a cold environment, emotional demands at work, influence at work, social support from supervisors, and social responsibility at work.

To conclude on the main aim of the PhD study, RA patients have increased risk of LTSA, with up to five times the risk of the general population during the first year of disease and twice the risk during subsequent years. RA patients have eight to 12 times increased risk of disability pension across e.g. gender, age and socio-economic status indicating that there is substantial room for further improvement in the handling of recent-onset and more established RA to reduce the risk of exclusion from the labour market in the future.

Perspectives

The present studies were conducted in order to extend our knowledge about risk and risk factor for long term sickness absence, unemployment and disability pension in patients with RA. This PhD thesis has provided insights into some aspects of the field, but several questions are relevant to address in future research projects:

- At the NRCWE, a new database has been developed for research purposes only: the Danish Register of Sickness absence compensation benefits and Social transfer payments (RSS)[71]. It contains detailed longitudinal information on social payments for all Danes from 2004, but is specifically made for analysis involving cases of sickness absence. It differs from DREAM in several aspects, for instance by the data structure, which is designed specifically for advanced survival analysis with analyses of multiple events, and by recording sickness absence on a daily basis and not weekly as in DREAM, which will reduce registration bias. For analyses of the risk of work related outcomes for RA patients from 2004 and onwards, it will be an advantage to use the RSS register to provide even more detailed information on the transitions between the different work related states of the multistate model, and by following RA patients in RSS after answering work related questionnaires.
- Use of disease variables from DANBIO (e.g. disability (HAQ), disease activity, health-related quality of life and medical treatments) would enable an estimate of the impact of these factors on risk and risk factors for long-term sickness absence, unemployment and disability pension.
- Measure self-reported work environment factors in patients who were working up to the time of diagnosis and again after one and two years to gain new knowledge about selection

into jobs with less physical strain, and/or to evaluate on the psychosocial working environment related to time of diagnosis.

- To investigate the RA patient's perception of RA in interviews, to identify their coping strategies and self-efficacy in relation to work, and to identify the processes that can lead to increased RA severity and exclusion from the labour market. This study would build on the knowledge obtained by the questionnaire used in paper III.
- Investigate whether different comorbidities affect the risk of long term sickness absence, unemployment and disability pension differently.

Summary in English

Rheumatoid arthritis (RA) is the most common of the inflammatory rheumatic diseases; it is a chronic joint disease, which may have severe impact on the patient's physical functioning and the ability to maintain a job. RA can occur at any age, but the incidence is highest in individuals of 40 and 60 years of age. Recent years have witnessed an increased interest in evaluating work related outcomes of RA such as long term sickness absence (LTSA), disability pension, unemployment and return to work. These outcomes are important both for the individual RA patients and from a societal perspective. For the individual, the LSTA often leads to reduced income and loss of contact with colleagues. Further, the individual has higher risk for permanent exclusion from the labor market. From a societal perspective, LTSA, disability pension and unemployment represents a significant loss of production and is a substantial economic burden.

The overall aim of this PhD project was to study the risk of long term sickness absence, unemployment, and disability pension in RA patients in Denmark, and thereby create new knowledge that could be used to keep RA patients in the labour market, and to provide the individual patient with better tools to manage the disease, by evaluating the association of work environment factors and LTSA.

The PhD project comprised of cohort studies, Cohort A and Cohort B:
Cohort A was a register study (Paper I and II) following 6,677 patients aged 18-59 years who were diagnosed with RA between year 1994 and 2011 and followed up until April 1st 2011 (Cohort A) They were compared with 56,955 controls from the general population matched by age, gender and city size. For paper I, the risk of LTSA was analyzed using Cox Proportional Hazards models with late entry, controlling for other risk factors and assuming separate risks in the first year after diagnosis and the following years. For paper II, the risk of LTSA, disability pension, unemployment and the chance of return to work was analyzed simultaneously in a multi-state model to calculate Hazard rates (HR). Analyses for paper I and II were stratified by disease duration, and included socio-demographic risk factors, physical job exposure, as well as somatic and psychiatric comorbidity.

Cohort B was a questionnaire study (Paper III) including of 895 patients with RA, aged 18-59 years by May 1st 2010, and working, who responded to a questionnaire in 2011 and were followed up in registers for two years. Respondents evaluated their work environment at baseline using standard occupational health questionnaires and rated their health and functioning using the SF-36v2 health survey. Sociodemographic data was collected through public registers and compared with a general population sample. Data on LTSA in the two years after baseline was collected through public registers. The risk of LTSA was analysed using proportional Hazards models.

In patients with RA, diagnosed between years 1994-2011 (Cohort A):
During the first year after diagnosis, the relative risk of LTSA for patients with RA was approximately five times higher than in the general population. During the subsequent years, the risk was twice as high as in the general population. Increased risk of LTSA was found for both unemployed RA patients and patients who were working prior to the LTSA (Papers I and II).

The excess high risk of LTSA decreased by approximately 20% in 2005-2011, compared to the period 1994-1999, for RA patients with more than one year's disease duration (Papers I and II). For both RA patients and the general population, short education and/or high physical job strain were risk factors for LTSA. Sero-positive RA patients had the same risk of LTSA as the sero-negative RA patients. RA patients with somatic or psychiatric co-morbidities had increased risk of LTSA compared to RA patients without, but the impact of co-morbidity in terms of relative risk was lower than in the general population (Paper I).

The chance of returning to work from LTSA or unemployment was markedly reduced for RA patients relative to the general person on LTSA or unemployment and this did not change between 1994-1999 and 2005-2011. The relative risk of unemployment for patients with RA was similar to or lower than for the general population both in early and more established disease (Paper II).

The relative risk of disability pension was eight to 12 times higher for RA patients compared to the general population (Paper II). However, from 1994-1999 to 2005-2011 the risk of disability pension for RA patients decreased relative to the general population (Paper II).

In patients with RA who were working in 2011 (Cohort B) the risks of LTSA was significantly increased for RA patients with high physical job demands and significantly lower for patients having high degrees of freedom at work and for patients working under a leadership they rated highly. Non-significant associations were found for working in a cold environment, emotional demands at work, influence at work, social support from supervisors, and social responsibility at work (Paper III).

RA patients have increased risk of LTSA, with up to five times the risk of the general population during the first year of disease and twice the risk during subsequent years. RA patients have eight to 12 times increased risk of disability pension across e.g. gender, age and socio-economic status indicating that there is substantial room for further improvement in the handling of recent-onset and more established RA to reduce the risk of exclusion from the labour market.

Dansk Resumé

Leddegigt (reumatoid artrit) er den mest almindelige af de inflammatoriske reumatiske sygdomme; Det er en kronisk ledsygdom, som kan have alvorlige konsekvenser for patientens fysiske funktion og evnen til at fastholde et job. Leddegigt kan forekomme i alle aldre, men forekomsten er højest hos personer imellem 40 og 60 år. I de seneste år har der været en øget interesse for at vurdere arbejdsrelaterede udfald af leddegigt såsom langtidssygefravær, invalidepension, arbejdsløshed og det at vende tilbage til arbejdet. Disse resultater er vigtige både for de enkelte leddegigtpatienter og fra et samfundsmæssigt perspektiv. For den enkelte patient kan langtidssygefravær føre til reduceret indkomst, og mistet kontakt med kolleger. Derudover har den enkelte patient højere risiko for permanent udelukkelse fra arbejdsmarkedet. Fra et samfundsmæssigt perspektiv repræsenterer langtidssygefravær, førtidspension og arbejdsløshed en betydelig økonomisk byrde.

Det overordnede formål med dette ph.d.-projekt var at undersøge risikoen for langtidssygefravær, arbejdsløshed og førtidspension hos leddegigtpatienter i Danmark og dermed skabe ny viden, der kunne bruges til at fastholde leddegigtpatienter på arbejdsmarkedet, og for at give den enkelte patient bedre redskaber til at håndtere sygdommen, ved at evaluere sammenhængen imellem arbejdsmiljøfaktorer og de arbejdsrelaterede udfald.

Ph.d.-projektet består af to kohortestudier, Kohorte A og Kohorte B:
Kohorte A var et registerstudie (artikel I og II) med 6.677 patienter i alderen 18-59 år, som blev diagnosticeret med leddegigt mellem 1994 og 2011 og fulgt indtil 1. april 2011. De blev sammenlignet med 56,955 kontroller fra den generelle befolkning, matchet på alder, køn og størrelsen af by. I artikel I blev risikoen for langtidssygefravær analyseret ved hjælp af Cox proportional Hazard modeller med ”late entry”, kontrolleret for andre risikofaktorer og stratificeret på sygdomsvarighed; det første år efter diagnose versus de følgende år efter diagnose. I artikel II benyttede vi en multi-state model som kunne estimere de relative risici for langtidssygefravær, førtidspension, og arbejdsløshed, og chancen for at vende tilbage til arbejde analyseret samtidigt. Analyserne for artikel I og II blev stratificeret på sygdomsvarighed, og omfattede socio-demografiske risikofaktorer, fysisk arbejdseksponering, samt somatisk og psykiatrisk ko-morbiditet.

Kohorte B var en spørgeskemaundersøgelse (artikel III), med 895 leddegigtpatienter, i alderen 18-59 år den 1. Maj 2010, som var i arbejde, og som svarede på et spørgeskema sendt i maj 2011. De

blev efterfølgende fulgt i registre i to år. Respondenternes arbejdsmiljø blev indsamlet og analyseret ved baseline ved hjælp af standard arbejdsmiljømæssige spørgeskemaer, og deres helbred og funktionsevne blev målt ved hjælp af SF-36v2 sundhedsundersøgelsen. Socio-demografiske data blev indsamlet via offentlige registre og sammenlignet med en kontrolpopulation fra den almene befolkning. Data om langtidssygefravær i de to år efter baseline blev indsamlet via offentlige registre. Risikoen for langtidssygefravær blev analyseret med proportional Hazard modeller.

Fra Kohorte A, som bestod af patienter med leddegigt, diagnosticeret mellem årene 1994-2011, var den relative risiko for langtidssygefravær for patienter med leddegigt ca. fem gange højere end i den almindelige befolkning i det første år efter diagnose. I løbet af de efterfølgende år, var risikoen dobbelt så høj som i den almindelige befolkning. Øget risiko for langtidssygefravær blev fundet for både arbejdsløse leddegigtpatienter og patienter, der arbejdede før langtidssygefravær (Artikel I og II).

Sammenlignet med perioden 1994-1999, var den forhøjede risiko for langtidssygefravær faldet med ca. 20% i 2005-2011 for leddegigtpatienter med mere end et års sygdomsvarighed (Artikel I og II). For både RA-patienter og den almindelige befolkning var kort uddannelse og/eller høj fysisk arbejdsbelastning risikofaktorer for langtidssygefravær. Sero-positive leddegigtpatienter havde samme risiko for langtidssygefravær som sero-negative leddegigtpatienter. leddegigtpatienter med somatiske eller psykiatriske ko-morbiditeter havde øget risiko for langtidssygefravær i forhold til leddegigt patienter uden, men virkningen af ko-morbiditet i form af en relativ risiko var lavere end i den almindelige befolkning (Artikel I).

Leddegigtpatienternes chance for at vende tilbage til arbejde fra langtidssygefravær eller fra arbejdsløshed var markant reduceret i forhold til kontrolpersonerne på langtidssygefravær eller med arbejdsløshed, og dette ændrede sig ikke fra 1994-1999 til 2005-2011. Den relative risiko for arbejdsløshed for patienter med leddegigt var magen til eller lavere end den for den generelle befolkning, både hos ny-diagnosticerede leddegigtpatienter og hos patienter som havde haft leddegigt i mere end et år (Artikel II).

Den relative risiko for førtidspension var otte til 12 gange højere for leddegigtpatienter i forhold til den almindelige befolkning (Artikel II). Men fra 1994-1999 til 2005-2011 faldt den relative risiko for invalidepension hos leddegigtpatienter i forhold til den almindelige befolkning (Artikel II).

Hos patienter med leddegigt, der arbejdede i 2011 (Kohorte B) var risikoen for langtidssygefravær signifikant forhøjet for leddegigt patienter med høje fysiske jobkrav og betydeligt lavere for patienter, der rapporterede en høj grad af frihed på arbejdspladsen og for patienter, der klassificerede deres nærmeste ledelse positivt. Vi fandt ikke signifikante sammenhænge for at arbejde i kolde omgivelser, følelsesmæssige krav i arbejdet, indflydelse på arbejdspladsen, social støtte fra vejledere, eller social ansvarlighed på arbejdspladsen (Artikel III).

leddegigtpatienter havde øget risiko for langtidssygefravær, med op til fem gange større risiko i forhold til den almindelige befolkning, i det første år af sygdommen og dobbelt så stor risiko i de efterfølgende år. RA-patienter havde otte til 12 gange øget risiko for førtidspension på tværs af fx køn, alder og socioøkonomisk status. Dette tyder på, at der er betydelig plads til yderligere forbedringer i forhold til håndteringen af leddegigt, både hos ny-diagnosticerede patienter og hos dem, som har haft leddegigt i længere tid, for at mindske risikoen for udelukkelse fra arbejdsmarkedet.

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Appendices

I: Paper I

II: Paper II

III: Paper III

IV: **Questionnaire “Arbejdsmiljøet for beskæftigede med RA”**

Paper I:

Paper I: Impact of Rheumatoid Arthritis on Long Term Sickness Absence in 1994-2011: A Danish Cohort Study

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Impact of Rheumatoid Arthritis on Long Term Sickness Absence in 1994-2011: A Danish Cohort Study

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ABSTRACT

Objectives: By linkage of national registries, we investigated the risk of long term sickness absence (LTSA) ≥3weeks in a large cohort of Danish rheumatoid arthritis (RA) patients and non-patientsThe study aimed to: 1. Estimate the risk of LTSA for RA patients compared to the general population, 2. Examine whether the risk of LTSA has changed in recent years, 3. Evaluate the impact of other risk factors for LTSA (e.g. physical work demands, age, gender, and education, psychiatric and somatic comorbidities).

Methods: A total of 6,677 RA patients aged 18-59 years in year 1994-2011 were identified in registries and compared with 56,955 controls from the general population matched by age, gender and city size. The risk of LTSA was analyzed using Cox Proportional Hazards models with late entry, controlling for other risk factors and assuming separate risks in the first year after diagnosis and the following years.

Results: Compared to the general population, RA patients had increased risk of LTSA in the first year after diagnosis (HR=5.4 during 1994-1999, 95%CI: 4.2-6.8) and in following years (HR=2.4, 95%CI: 2.1-2.8). For established RA (>1 year after diagnosis) the excess was 20% lower in 2006-2011 (HR=1.9, 95%CI: 1.7-2.2) compared to 1994-1999 (P<0.001). For RA patients and controls, higher age, shorter education, a physically demanding job, and somatic and/or psychiatric comorbidities increased the risk of LTSA.

Conclusions: While improvements were observed from 1994-1999 to 2006-2011, patients with RA have significant increased risk of LTSA, in particular in the first year after diagnosis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease, which has large impact on the patient's physical function and somatic and mental health. Two-thirds of individuals who get RA are at working age[1] and therefore risk long-term sickness absence (LTSA) and work disability. The risk seems to be highest in the first year after RA diagnosis and stabilizes at a lower level with small annual increases during the subsequent years[2;3]. During the past 15 years, the treatment of RA has changed towards earlier and more aggressive treatment with synthetic and biologic disease-modifying anti-rheumatic drugs (DMARDs)[4-7]. This appears to have reduced the risk of LTSA[2;3]. In addition to RA severity and duration, the risk of LTSA may also be influenced by personal and environmental factors such as gender, age, lifestyle, physically demanding jobs, lower educational level, and socio-economic status[7-9]. LTSA is an important outcome for patients with RA, both from an individual and a societal perspective. For the individual patient, LTSA often leads to reduced income and loss of contact with colleagues. Further, LTSA puts the patient at higher risk for permanent exclusion from the labor market. From a societal perspective, LTSA represents a significant loss of production and is a substantial economic burden[10]. By linkage of national registries in Denmark we investigated for the first time simultaneously several aspects of the risk of LTSA in a large cohort of patients with RA. The aims of this study were: 1. To estimate the risk of LTSA for patients with RA compared to the general population, 2. To study if the risk of LTSA has changed over the last decades, and 3. To evaluate the impact of other risk factors for LTSA, such as physically demanding jobs, gender, education and comorbidities.

METHODS

Data sources

We identified RA patients from the nationwide DANBIO registry and The Danish National Patient Registry (NPR) and matched them with controls from the general population. DANBIO is a nationwide registry that provides data on the disease course of adult patients with inflammatory rheumatic joint diseases[11-13]. The NPR includes all hospital admissions (since 1977) and outpatient activities (since 1995) in Denmark, and patients are registered by diagnoses according to the International Classification of Diseases codes (1978-1993: ICD-8; 1994-2011: ICD-10)[14]. The NPR was also used to identify co-morbidity, in combination with the Danish National Prescription Registry (PRESCRIBE), which provide information on all prescribed medications dispensed from Danish pharmacies since 1995. We were not able to obtain information about biological treatment, since biologic drugs are dispensed by the hospitals and not registered in PRESCRIBE.

We retrieved individual data on LTSA from the DREAM register, which provides weekly information on social transfer payments for all residents in Denmark (since July 1991). It is based on data from the Danish ministries of Employment, Social Affairs, and Education, and has been shown to be suitable for follow-up of social consequences of disease[15]. To be eligible for sickness absence benefit the employee must have worked minimum 120 hours during the last 13 weeks[16].

Data from these registers were linked through the central personal register (CPR) number, a unique personal identifier given at birth to all Danes.

The study cohort: RA patients and controls

From DANBIO, which has an estimated coverage of 79%, we identified a cohort of RA patients aged 18-59 years at the time of RA diagnosis and who got the disease between 1991 and 2011, N = 4865[17]. For each patient, 10 controls from the general population were identified in the nationwide registers of Statistics Denmark, matched on gender, age and city size. To identify additional RA patients that were not registered in DANBIO, the control group was screened in the NPR for individuals who had been hospitalized or received outpatient treatment with an RA diagnosis three or more times. This has been shown to be a valid approach to identify RA patients in the NPR[18]. Thus, the following codes from ICD-8 and ICD-10 were used: 712.19 (Syndroma Felty), 712.39 (Arthritis rheumatoides alia et non specificata), 712.59 (Fibrositis rheumatoides chronica nodularis), DM05 (Arthritis rheumatoides seropositiva), DM06 (Arthritis rheumatoides alia) except DM06.1 (Still's disease)[18]. Such patients (N=1,812) were included in the RA group and excluded from the control group (Total number of RA patients = 6677). Individuals with uncertain RA status (i.e. only one or two relevant RA diagnoses in the NPR) were excluded from the analysis. The controls were then re-matched to the merged population, by gender, age and city size, leading to a minimum of 8 controls per patient and a maximum of 10 controls per RA patient, the median being 9 controls per RA patient. In sensitivity analysis, comparing results with and without RA patients from NPR, we found no difference in HR, but increased estimate precision when NPR patients were included.

Primary outcome variable

Individuals were classified as having LTSA if receiving sickness absence benefits for a period of at least 3 weeks. Briefly, this definition was used because, the sickness absence became registered in DREAM at 3 or more weeks of sickness absence, when the municipalities became responsible for

managing the sickness absence cases[19;20]. Follow up started January 1st 1994 and ended April 1st 2011.

Covariates

Ten variables were included in the analysis: 1. Rheumatoid arthritis classified as sero-negative (including non-specific RA), or sero-positive; 2. Calendar year (1994-1999, 2000-2005, or 2006-2011); 3. Gender; 4. Age (18-29, 30-39, 40-49, or 50-59 years); 5. Immigrant status (immigrant, immigrant descendent, or Danish); 6. Household composition (Single or cohabitants with or without children, including singles living with children); 7. City size (capital centre, closest suburbs, the metropolitan area, city > 100,000 inhabitants, city 10,000 – 100,000 inhabitants, or the rest of the country); 8. Highest obtained education (At most high school, Vocational training, Tertiery/Polytecnic school, Higher education (e.g. Master, PhD)); 9. Physical job exposure (0 kg/day, 1-5999 kg/day, > 6000 kg/day); 10. Somatic and psychiatric co-morbidities. In addition, we controlled for seasonal variations in LTSA.

To control for diseases that could be competing causes of LTSA, we adjusted for 18 groups of chronic, somatic comorbidities (cancer, thyroid diseases, diabetes, other endocrine, nutritional and metabolic diseases, obesity, neurological diseases, chronic diseases of the ears, hypertension, chronic pulmonary diseases including asthma, cardiac disease, stroke, inflammatory bowel disease, diseases of the liver, diseases of the skin, kidney diseases, gynecological diseases, and transplantations) and 4 groups of psychiatric comorbidities (dementia, substance abuse, anxiety, and depression). These comorbidities were selected by an expert panel prior to data analysis.

Physical job exposure was estimated from job type (retrieved from DREAM) using a job exposure matrix based on the Danish version of the International Standard of Classification of Occupations (DISCO-88[14;21]). The job exposure matrix is described elsewhere[22;23]. For the present study,

physical job exposure was categorized into three groups according to estimated kilograms lifted per work day: 0 kg/day, 1-5999 kg/day, > 6000 kg/day.

All variables except gender and immigrant status were treated as time-dependent variables, thus taking into account that individuals may change status during the period of observation.

Analysis

The hazard ratio of LTSA for employees was estimated using the Cox Proportional Hazards model (SAS 9.2 PROC PHREG) with latent entry, i.e. the patient was included in the analysis when he or she was diagnosed with RA, and the matched controls appeared at the same time. LTSA was treated as a repeated event by the use of a frailty model[24;25]. Using frailty models is the common way to quantify the person variation that arises when persons have more than one period of LTSA. It allows dependence of multiple events in the analysis, and it handle the heterogeneity in this type of dataset when estimating hazards [25] A priori, our analyses of LTSA assumed separate risks in; 1) the first year after diagnosis, 2) the subsequent years after diagnosis. The assumption of proportionality has been investigated by visual inspection of cumulative hazard curves for each covariate.

Subjects were censored if they died, turned 60 years, emigrated, became unemployed, received disability pension or at the end of the observation period (2011), whichever came first. Subjects were temporarily out of risk if they were on maternity leave, other kinds of leave, or students. Initial analyses were performed separately for the two genders, but since the results were similar, the final analysis was performed on the combined population, controlling for gender. We analyzed the risk of LTSA for sero-negative and sero-positive RA patients and found no difference. Thus, the two groups were combined in the final analysis. We analyzed the hazard ratio in three models of increasing complexity. In model 1, analyses were controlled for sociodemographic confounders

(age, gender, ethnicity, urbanization, highest obtained education, and family type). In model 2, we also controlled for somatic and psychiatric comorbidities. In model 3, interactions between rheumatoid arthritis and all the covariates were added as well, one at a time. Only results that were significant are shown (interactions between RA and calendar year, gender, and somatic and psychiatric comorbidities). Each analysis was controlled for the ten covariates.

Ethics approval

The study was approved by The Danish Data Protection Agency, journal number: 2015-41-3828.

RESULTS

Sample characteristics

Table 1 describes the characteristics of the study population at entry. Age, gender, household status, level of education, physically demanding jobs and urbanization were largely similar between patients and controls, whereas more patients were of Danish origin. Compared to the controls, more patients suffered from somatic, but not psychiatric, comorbidities.

Table 1. Characteristics of patients with rheumatoid arthritis and of the controls when entering the study

		RA population	Control population
		% (N = 6,677)	% (N = 56,955)
Year of diagnosis	1994 - 1999	38.5	-
	2000 - 2005	31.9	-
	2005 - 2011	29.6	-
Gender	Female	73.6	73.3
	Male	26.4	26.7
Age	≤ 29 years	7.5	7.2
	30-39 years	18.7	19.7
	40-49 years	33.1	33.8
	50-59 years	40.8	39.3
Immigrant status	Danish	94.6	87.0
	Immigrant	5.2	12.8
	Descendants	0.3	0.2
Household composition	Cohabitants with or without children, and singles living with children	77.4	77.3
	Singles	22.6	22.7
City size	Capital centre	14.1	12.6
	Closest suburbs	13.9	15.5
	The metropolitan area	6.5	7.6
	City > 100,000	9.9	12.1
	City 10,000 – 100,000	29.4	27.5
	The rest of the country	26.2	24.8
Highest obtained education	At most high school	33.7	33.2
	Vocational training	39.6	35.8
	Tertiary/polytechnic school	20.9	22.2
	Higher education (e.g. Master, PhD)	4.2	5.9

	NA	1.6	2.9
Physical job exposure	0	43.3	44.5
Estimated kg lifted per day	1-5999	31.5	32.3
	≥ 6000	25.2	23.2
Somatic Comorbidity	0	69.4	75.7
	≥1	30.6	24.3
Psychiatric Comorbidity	0	91.3	92.2
	≥1	8.7	7.8

Events of LTSA

For RA patients, 983 events (start of LTSA) were observed in the first year after diagnosis (out of 2735 person years (PY) of observation). Thus, the rate of LTSA was 0.36 events/PY. In subsequent years, 2951 events were observed during 19,577 PY for a rate of 0.15 events/PY. For controls, 2417 events were observed within the first year of diagnosis of the index patient (out of 30,399 PY, rate= 0.08 events/PY). In subsequent years, 21,404 events were observed during 266,270 PY for a similar rate of 0.08 events/PY.

Cumulative hazards stratified by calendar years

Figure 1 shows the cumulative hazards (risk of LTSA) for the two groups stratified on the three periods, with separate graphs for the first year after diagnosis (Figure 1A) and subsequent years (figure 1B). For the control group, the cumulative hazards increased from 1994-1999 to 2000-2005 and also increased slightly from 2000-2005 to 2006-2011. The RA group followed the same pattern for the periods 1994-1999 and 2000-2005, whereas the 2006-2011 period showed lower cumulative hazards than 2000-2005.

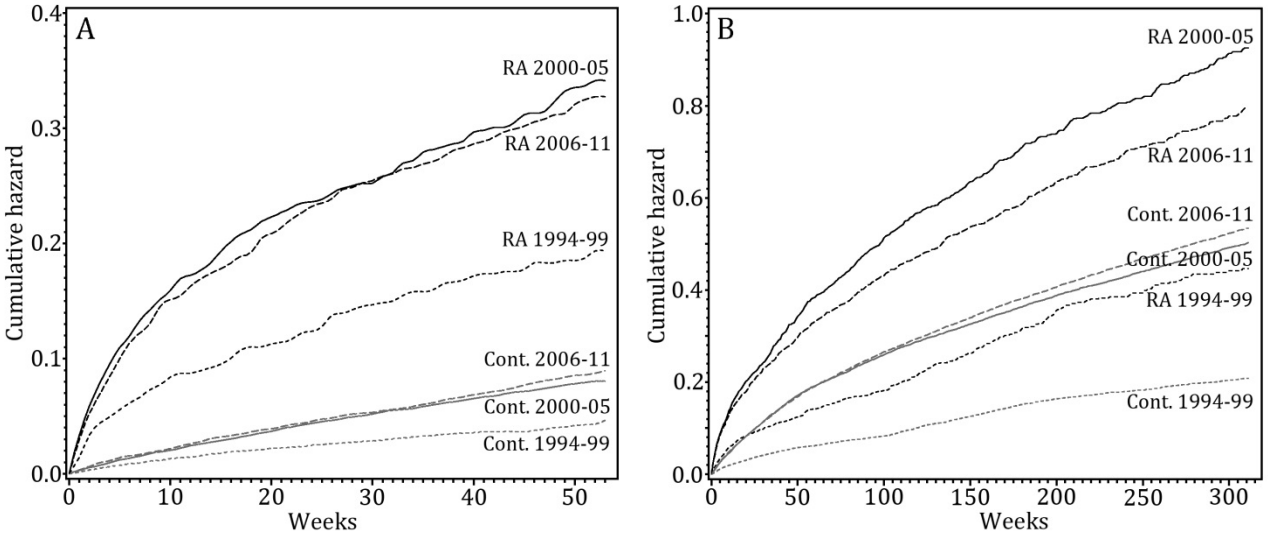

Figure 1, Cumulative Hazard for long-term sickness absence in patients with RA and their controls. Stratified by calendar year of diagnosis; A: The cumulative hazards for the first year after RA diagnosis; B: The cumulative hazards for following years: The cumulative hazards for the controls are calculated from the time of diagnosis of their matched RA patient. Note that figure A is on a scale from 0.0 to 0.4, and 52 weeks, while figure B is on a scale from 0.0 to 1.0, and 312 weeks.

Risk of long-term sickness absence - Model 1

Patients with RA had a hazard ratio of LTSA of 4.1 in the first year after diagnosis (Table 2, model 1) and of 1.8 in subsequent years (Table 3, model 1), compared to the general population. In general, risk of LTSA was higher in the years 2000-2005 and 2006-2011 compared to 1994-1999. Also, the risk was lower for men than for women. The risk of LTSA decreased with higher educational level with a HR of approximately 0.5 for individuals with at least a college degree compared to those with only elementary schooling or high school degree. A physically demanding job significantly increased the risk of LTSA.

Table 2. Results from analyses by proportional hazards models of long term sickness absence during the first year after diagnosis with rheumatoid arthritis

	Model 1		Model 2		Model 3	
Variable	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Rheumatoid arthritis[a]						
No	1		1		1	
Yes	4.1***	(3.8-4.5)	4.0***	(3.6-4.3)	5.4***	(4.2-6.8)
Calendar year						
1994-1999	1		1		1	
2000-2005	1.8***	(1.7-2.0)	1.6***	(1.5-1.8)	1.7***	(1.5-1.9)
2006-2011	2.0***	(1.8-2.2)	1.7***	(1.5-1.9)	1.7***	(1.5-2.0)
Gender						
Female	1		1		1	
Male	0.7***	(0.6-0.7)	0.7***	(0.6-0.8)	0.7***	(0.6-0.7)
Highest obtained education						
Elementary school/high school	1		1		1	
Vocational training	1.0	(0.9-1.0)	1.0	(0.9-1.1)	1.0	(0.9-1.0)
Tertiary/polytechnic school	0.8***	(0.8-0.9)	0.8***	(0.8-0.9)	0.8***	(0.7-0.9)
Higher education (e.g. Master, PhD)	0.4***	(0.3-0.5)	0.4***	(0.3-0.5)	0.4***	(0.3-0.5)
NA	1.2	(1.0-1.6)	1.2	(1.0-1.6)	1.2	(1.0-1.6)
Physical job exposure (kg/day)						
0	1		1		1	
1-5999	1.6***	(1.5-1.8)	1.6***	(1.5-1.8)	1.6***	(1.5-1.8)
≥ 6000	2.0***	(1.8-2.2)	1.9***	(1.8-2.1)	1.9***	(1.7-2.1)
Somatic comorbidity[b]						
No	-		1		1	
Yes	-		1.5***	(1.4-1.6)	1.6***	(1.5-1.8)

Psychiatric comorbidity					
No	-	1		1	
Yes	-	2.0***	(1.8-2.2)	2.2***	(2.0-2.5)
Rheumatoid arthritis x calendar year					
1994-1999	-	-		1	
2000-2005	-	-		1.0	(0.8-1.2)
2006-2011	-	-		0.9	(0.7-1.1)
Rheumatoid arthritis x gender					
Female	-	-		1	
Male	-	-		1.1	(0.9-1.3)
Rheumatoid arthritis x somatic comorbidity[b]					
No	-	-		1	
Yes	-	-		0.7**	(0.6-0.9)
Rheumatoid arthritis x psychiatric comorbidity					
No	-	-		1	
Yes	-	-		0.6***	(0.4-0.7)

All analyses were controlled for age, ethnicity, urbanization, season, and family type
[a] Patients with RA (N=6,677) and matched controls (N=56,955)
[b] Somatic morbidity except rheumatoid arthritis
* < 0.05 ** <0.01 *** < 0.001

Risk of long-term sickness absence - Model 2

In model 2, the risk for LTSA was higher for persons with somatic or psychiatric comorbidity, but the inclusion of these variables did not change the risk estimates for RA (Tables 2 and 3, model 2).

Risk of long-term sickness absence - Model 3

Significant interactions were found between RA and gender, calendar year, somatic, and psychiatric comorbidities (Table 2 and 3). We also tested for interactions between RA and the other covariates as well as between education and physical job exposure, but did not find significant results. The hazard ratio of LTSA during the years 1994-1999 for a woman with RA and no comorbidity was 5.4 (95% C.I.:4.3-6.8) in the first year after diagnosis and 2.4 (2.1-2.8) in subsequent years (table 2 and 3, model 3). The interaction effect was <1 between RA diagnosis and the years 2000-2005 and 2006-2011. Thus, the excess risk of LTSA in patients with RA through more than 1 year was reduced by 20% (HR= 0.8 (0.7-0.9)) in the years 2006-2011 compared to 1994-1999 (Table 3). These interaction effects were not significant in the first year after diagnosis, but highly significant in subsequent years (P<0.001, Table 3). An interaction effect above 1 between male gender and RA through more than a year (P<0.05, Table 3) indicates that the gender difference in LTSA was less pronounced among RA patients than among the general population. We found interaction effects < 1 between RA diagnosis and somatic and psychiatric comorbidities, which reflected that although RA diagnosis as well as other somatic and psychiatric diseases increased the risk of LTSA, the interaction effect was less than the product of the individual effects.

Table 3. Results from analyses by proportional hazards models of long term sickness absence more than one year after diagnosis with rheumatoid arthritis

	Model 1		Model 2		Model 3	
Variable	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Rheumatoid arthritis[a]						
No	1		1		1	
Yes	1.8***	(1.7-1.9)	1.8***	(1.8-1.9)	2.4***	(2.1-2.8)
Calendar year						
1994-1999	1		1		1	
2000-2005	2.3***	(2.1-2.4)	2.0***	(1.9-2.1)	2.0***	(1.9-2.1)
2006-2011	2.3***	(2.2-2.4)	1.9***	(1.8-2.0)	2.0***	(1.8-2.1)
Gender						
Female	1		1		1	
Male	0.7***	(0.7-0.7)	0.8***	(0.7-0.8)	0.7***	(0.7-0.8)
Highest obtained education						
Elementary school/high school	1		1		1	
Vocational training	0.9***	(0.9-1.0)	0.9***	(0.9-1.0)	0.9***	(0.9-1.0)
Tertiary/polytechnic school	0.8***	(0.8-0.9)	0.8***	(0.8-0.9)	0.8***	(0.8-0.9)
Higher education (e.g. Master, PhD)	0.5***	(0.5-0.6)	0.5***	(0.5-0.6)	0.5***	(0.5-0.6)
NA	1.0	(0.9-1.1)	1.0	(0.9-1.1)	1.0	(0.9-1.1)
Physical job exposure (kg/day)						
0	1		1		1	
1-5999	1.4***	(1.3-1.4)	1.4***	(1.3-1.4)	1.3***	(1.3-1.4)
≥ 6000	1.6***	(1.5-1.6)	1.5***	(1.5-1.6)	1.5***	(1.5-1.6)
Somatic comorbidity[b]						
No	-		1		1	
Yes	-		1.5***	(1.5-1.6)	1.5***	(1.5-1.6)
Psychiatric comorbidity						
No	-		1		1	

Yes	-	1.9***	(1.8-1.9)	1.9***	(1.8-2.0)
Rheumatoid arthritis x calendar year					
1994-1999	-	-		1	
2000-2005	-	-		0.9	(0.8-1.1)
2006-2011	-	-		0.8***	(0.7-0.9)
Rheumatoid arthritis x gender					
Female	-	-		1	
Male	-	-		1.1*	(1.0-1.3)
Rheumatoid arthritis x somatic comorbidity[b]					
No	-	-		1	
Yes	-	-		0.8***	(0.7-0.9)
Rheumatoid arthritis x psychiatric comorbidity					
No	-	-		1	
Yes	-	-		0.8**	(0.7-0.9)

All analyses were controlled for ethnicity, urbanization, season, and family type
[a] Patients with RA (N=6,677) and matched controls (N=56,955)
[b] Somatic morbidity except rheumatoid arthritis
* < 0.05 ** <0.01 *** < 0.001

Impact of certain risk factors on LTSA in RA - The interaction parameters

Table 4 illustrates the implications of the interaction parameters from model 3 in Table 2 and 3 for comparisons between RA patients with and without certain risk factors. For example, RA patients with psychiatric comorbidity had a 1.2 hazard ratio of LTSA within the first year of diagnosis compared to RA patients without psychiatric comorbidity. In subsequent years, the hazard ratio was 1.5.

Table 4. Hazard ratios for long term sickness absence for patients with rheumatoid arthritis with or without particular risk factors[a]

		First year		Subsequent years	
Variable		HR	(95% CI)	HR	(95% CI)
Calendar year	1994-1999	1		1	
	2000-2005	1.6	(1.3-2.0)	1.9	(1.6-2.2)
	2006-2011	1.5	(1.3-1.9)	1.6	(1.3-1.8)
Gender	Female	1		1	
	Male	0.7	(0.6-0.9)	0.8	(0.8-0.9)
Somatic comorbidity	No	1		1	
	Yes	1.2	(1.0-1.4)	1.3	(1.1-1.4)
Psychiatric comorbidity	No	1		1	
	Yes	1.2	(1.0-1.5)	1.5	(1.3-1.7)
Highest obtained education	Elementary school/high school	1		1	
	Vocational training	1.0	(0.9-1.0)	0.9	(0.9-1.0)
	Tertiary/polytechnic school	0.8	(0.7-0.9)	0.8	(0.8-0.9)
	Higher education (e.g. Master, PhD)	0.4	(0.3-0.5)	0.5	(0.5-0.6)
	NA	1.2	(1.0-1.6)	1.0	(0.9-1.1)
Physical job exposure Kg/day	0	1		1	
	1-5999	1.6	(1.5-1.8)	1.3	(1.3-1.4)
	≥ 6000	1.9	(1.7-2.1)	1.5	(1.5-1.6)

[a] For risk factors where an interaction effect was found, the combined effect was calculated as the product of the interaction and the main effect (e.g. the HR in the first year after diagnosis for RA patients in 2006-2011 compared to 1994-1999 was calculated as the product of the HR for 2006-2011 (= 1.7) and the RA * period interaction effect (=0.9) – table 2).

Combination of risk factors for LTSA in RA compared with controls

Table 5 compares the risks within particular risk groups or years for persons with RA compared with controls – based on the parameters from model 3. For any combination of risk factors for LTSA, an RA diagnosis constituted a considerable additional risk factor both in the first year after diagnosis (HR:2.7-5.4) and in subsequent years (HR:1.5-2.4).

Table 5. Hazard ratios for long term sickness absence for rheumatoid arthritis patients compared to the general population for different combinations of risk factors[a]

				Rheumatoid arthritis			
				First year		Subsequent years	
Variable		Status on other variables	General population	HR	(95% CI)	HR	(95% CI)
Calendar year	1994-1999	Female no somatic or psychiatric comorbidities	1	5.4	(4.2-6.8)	2.4	(2.1-2.8)
	2000-2005		1	5.1	(4.3-6.3)	2.3	(2.0-2.5)
	2006-2011		1	4.8	(4.0-5.8)	1.9	(1.7-2.2)
Gender	Female	Year 2006-2011 no somatic or psychiatric comorbidities	1	4.8	(4.0-5.8)	1.9	(1.7-2.2)
	Male		1	5.2	(4.1-6.5)	2.2	(1.9-2.5)
Somatic comorbidity	No	Female, year 2006-2011, no psychiatric comorbidities	1	4.8	(4.0-5.8)	1.9	(1.7-2.2)
	Yes		1	3.6	(3.0-4.3)	1.6	(1.4-1.7)
Psychiatric comorbidity	No	Female, year 2006-2011, no somatic comorbidities	1	4.8	(4.0-5.8)	1.9	(1.7-2.2)
	Yes		1	2.7	(2.0-3.5)	1.5	(1.3-1.8)

[a] The combined effect was calculated as the product of the relevant interaction and main effects (e.g. the HR in the first year after diagnosis for RA patients in 2006-2011 compared to the general population was calculated as the product of the HR for RA in 1994-1999 (= 5.4) and the RA * period interaction effect (=0.9) – table 2).

DISCUSSION

Our results show that RA patients had substantially increased risk of LTSA, both in the first year after diagnosis and in subsequent years. Thus, in the years 2006-2011, a woman with RA had a hazard ratio of 4.8 for LTSA in the first year after diagnosis, and a hazard ratio of 1.9 in subsequent years. These results are in line with previous studies[2;3], but the large size of our study allowed more precise estimation of the risk and more detailed analyses of potentially modifiable factors.

For both patient and the general population, the risk of LTSA increased from 1994-1999 to 2000-2005 probably due to changing conditions in the Danish labour market (with a possible additional effect of improved registration [26]). The risk remained high for the general population during 2006-2011, but decreased for RA patients – in particularly over a year after diagnosis. The hazard ratio of LTSA for patients with RA was reduced by 20% when we compared recent years (2006-2011) with the earliest period of observation (1994-1999). Previous studies have shown positive results of treatment with biological drugs on LTSA. In a cohort study comparing RA patients starting biological treatment with the general population, a decrease of almost 30% in LTSA was observed during the first year of biological treatment[27]. The study only included RA patients who completed the biological treatment, which may have biased the result. Also, a decrease in LTSA as a result of treatment with biologics was shown in two RCT studies [28;29]. In the first study, the odd for favorable employment status was ≈1.5 in patients treated with combination treatment (adalimumab + methotrexate (MTX)) versus MTX alone[29]. In the second study, combination treatment (certolizumab pegol plus MTX) led to a cumulative annual gain of ≈ 40 full work days and ≈30 fewer days with reduced productivity compared to placebo plus MTX[28]. These results suggest that modern treatment strategies including, but not limited to[30;31], the use of biologics, reduce LTSA for RA patients. In our study, however, we did not have access to data that could support this hypothesis. Other factors may also have influenced the risk of LTSA, e.g. improved

treatment strategies also for conventional drugs, earlier diagnosis, and advances on health education programs.

Similar to the general population, patients with RA with short education and/or high physical strain at work had an increased risk of LTSA. This is an important finding, since level of education and the amount of physical job strain are potentially modifiable factors. Other important risk factors identified in our study (age, family type, and education), also influenced the risk for LTSA similarly for RA patients and the general population, and therefore are not specific for patients with RA. Generally, females had a higher risk of LTSA than males, and although this was also the case for RA patients, the difference between male and female RA patients was less than in the general population. We had expected the risk to be higher for patients with sero-positive RA, but this was not the case. We did not have access to data on anti-CCP status. Patients with RA and somatic or psychiatric comorbidity had a higher risk for LTSA than patients without, but the risk ratios were lower for RA patients than for the general population.

A major strength of the study is that it was a cohort study based on a nationwide registry, including >6,600 patients with RA at working age in Denmark, who were compared to a large control group of 8-10 persons per RA patient. This enabled us to calculate the hazard ratio of LTSA for RA patients. Importantly, we investigated changes in risk across the decades, during which the treatment of RA changed to earlier and more aggressive treatment strategies. This was made possible by the combined use of administrative databases with high coverage[15;18] and the DANBIO registry with diagnoses of high validity[13].

The increase in hazard ratio of LTSA for RA patients was robust even after controlling for a large number of covariates. Although residual confounding may exist, the results show that individuals who get RA have up to five times increased risk of LTSA across e.g. gender, age and socio-

economic factors during the first year of disease, indicating that there is substantial room for further improvement in the handling of recent-onset RA.

We had expected physical job exposure to be a specific risk factor for RA patients, but this was not the case in our analyses. Physical exposure was defined using job codes linked with amount of kg lifted per day. This is a good proxy for physically demanding jobs[22;23], but it may not be the ideal way to define hard work for RA patients, who may have greater trouble with gripping and with fine movements of the hands. DANBIO contains high-quality records of the patients' disease course since year 2000, but since we did not have those data for the preceding years of our study period, we chose not to include them. Future studies may evaluate the impact of other disease specific variables on the hazard ratio of LTSA. Our patient group may be influenced by selection bias, because DANBIO started in year 2000; i.e. RA patients between 18 and 59 years old, who died between 1994 and 1999, were not registered in DANBIO and only included in the study if identified from the NPR controls. Since such patients would be expected to have serious illness, our risk estimate for LTSA for the period 1994-1999 and the reduction in HR from 1994-1999 to 2006-2011 may be underestimated.

In conclusion, RA increased the risk of LTSA approximately five times during the first year after diagnosis and twice during subsequent years compared to the general population. Compared to 1994-1999, the excess long-term risk after the first year after diagnosis decreased by approximately 20 % in 2006-2011.

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Paper II:

Impact of Rheumatoid Arthritis on Work Ability: A register study on the Prospective Risk of Long Term Sickness Absence, Unemployment, and Disability Pension, and of Probability for Return to Work

Submitted

Impact of Rheumatoid Arthritis on Work Ability: A register study on the Prospective Risk of Long Term Sickness Absence, Unemployment, and Disability Pension, and of Probability for Return to Work

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ABSTRACT (words 249)

Objectives: To study the impact of rheumatoid arthritis (RA) on work ability by investigating 1) the rates and risks of long term sickness absence, unemployment, and disability pension, as well as the chance of return to work compared to a matched control population and 2) the changes in these risks over time (1994-2011) as an indicator of the possible effect of modern treatment strategies.

Methods: A cohort study with 17 years' follow-up (mean 6.95 years/person) including 6,677 RA patients at working age identified in the nationwide DANBIO registry, and 56,955 matched controls. A multi-state model was used to analyze all shifts between the work-related states simultaneously and calculate Hazard rates (HR). Analyses were stratified by disease duration, and controlled for socio-demographic factors, physical job exposure, as well as somatic and psychiatric comorbidity.

Results: The RA patients had increased risk of long term sickness absence (e.g. early RA: HR=4.00 (95% Confidence Intervals 3.64-4.30) and disability pension (e.g. established RA: HR=2.75(2.54-2-98)) relative to controls. The relative risks of long term sickness absence and disability pension decreased from 1994-99 to 2006-11 (e.g. established RA: HR 2.25(1.99-2.54) to 1.63(1.51-1.75)). RA patients had a lower chance of returning to work from long term sickness absence (early RA: HR=0.60(0.55-0.66)) or unemployment (early RA: HR=0.77(0.70-0.85)), and this did not change over time.

Conclusions: RA patients remain at high risk for long term sickness absence and disability pension, but a positive trend is seen from 1996-1999 to 2006-2011. Returning to work remains a challenge for RA patients.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease with potentially severe impact on the patients' physical function and work ability. Two-thirds of those contracting RA are at working age.[1] This makes long term sickness absence, unemployment and early retirement some of the most important outcomes of the disease, both for the patient and for society.[2] Modern treatment strategies in RA have developed since year 2000, involving close monitoring of disease activity and more aggressive treatment to achieve remission [3] through the use of synthetic and biologic disease-modifying anti-rheumatic drugs (DMARDs).[4-6] We have reported that the more aggressive treatment strategies of RA since year 2000 are associated with a decrease in the risk of long term sickness absence both in the first year after the first RA diagnosis and in the subsequent years. However, the risk is still 2 to 4 times higher than in the general population.[7] Historically, RA patients have an increased risk of permanent loss of work ability, resulting in disability pension.[8-10] A decrease in the risk of disability pension during later years has been reported, but it is not known whether it merely reflected a reduction in disability pension in general, caused by political, demographic, and socioeconomic changes, or represented a disease-specific decline e.g. due to modern treatment strategies.[4] The same uncertainty applies to the risk of unemployment and return to work for patients with RA.

In patients diagnosed with RA between 1994 and 2011, who were treated in routine care, we therefore aimed to study in a multi-state model: 1) all shifts between work, long term sickness absence, unemployment, and disability pension (see figure 1) compared to a matched control population, and 2) the changes in these risks over time as an indicator of a possible effect of modern treatment strategies.

[Figure 1 about here]

We conducted both univariate analyses and multivariate analyses controlling for socio-demographic factors, physical job exposure, and somatic and psychiatric comorbidity. Results were stratified by disease duration, since we expected different risks during the first year of disease and subsequent years.

METHODS

Data sources

The data sources have been described in detail previously.[7] Briefly, we identified a total of 6,677 RA patients of working age (i.e. 18-59 years) from the nationwide DANBIO registry, a register on adult patients with inflammatory joint diseases (e.g. RA),[11-13] and from The Danish National Patient Registry (NPR). The patients were matched by gender, age and size of resident city, with 8-10 controls from the general population. Among the controls, 1,812 patients with RA were identified and included in the patient cohort.[14] The NPR was also used to identify co-morbidity, in combination with the Danish National Prescription Registry (PRESCRIBE).[7]

We retrieved individual data on the work-related outcomes from the DREAM register, which provides weekly information on social transfer payments for all residents in Denmark (since July 1991). Physical job exposure was estimated from job type using a job exposure matrix based on the Danish version of the International Standard of Classification of Occupations (DISCO-88).[15-17] Data from these registers were linked through the central personal register (CPR) number, a unique personal identifier given at birth to all Danish citizens.

Primary outcome variables

The primary outcome variables were: Long term sickness absence, unemployment, return to work and disability pension. Individuals receiving sickness absence benefit for a period of at least three weeks were classified as being on long term sickness absence. Individuals receiving different

unemployment benefits were collectively classified as being unemployed. Persons receiving disability pension or working on special terms, such as flexible job or receiving early retirement pension, were classified as receiving disability pension. Persons who did not receive any benefits (including house wives) were classified as working.[2] The study period started on January 1st 1994 and follow-up ended on April 1st 2011.

Covariates

Eleven variables were included as covariates in the statistical analyses (see table 1 for details): Rheumatoid arthritis, gender, age group, size of resident city, year of diagnosis, immigrant status, household composition, highest obtained education, physical job exposure, somatic and psychiatric co-morbidities.[7] In addition, we corrected for seasonal variations.

All variables except gender and immigrant status were treated as time-dependent variables, thus taking into account that individuals may change status during the period of observation.

Multi-state model

Figure 1 illustrates the possible shifts in work status on the labour market. The present study analyzed the shifts between being at work, on long term sickness absence, unemployed, and receiving disability pension, respectively. We refer to the shifts as *transitions* (arrows at figure 1, #1 to #9), and to the work-related outcomes as *states*. In the model, the participants can leave and reenter the states work, long term sickness absence, and unemployment through the study period, so these states were treated as transient states. When a person received disability pension, he or she was not at risk for further transitions, so the state disability pension was treated as an absorbing state.[2, 18] If a person moved to other kinds of work-related states (e.g. maternity leave or studying), he or she was temporarily out of risk. Subjects were censored if they died, turned 60

years of age, emigrated, or reached the end of the observation period (April 1st 2011), whichever came first. Based on person years (PY) and the number of events, we calculated the rates of the different transitions (events/1000 PY). The mean follow up time per person was 6.95 years/person in the 17 years' follow-up period.

The patients were included in the analysis when they were diagnosed with RA, and the matched controls appeared at the same calendar time. A priori, our analyses assumed separate risks in the first year after diagnosis and in the subsequent years, so all results are presented stratified by disease duration. Initial analyses were performed separately for the two genders, but since the results were similar (data not shown), the final analyses were performed on the combined population, controlling for gender. We analysed the risk of long term sickness absence for sero-negative and sero-positive RA patients and found no difference (data not shown). Thus, the two groups were combined in the analyses of all transitions.

Initial analyses evaluated the number of PY in each state, the number of transitions to other states, and the rate for each transition. In the multivariate analyses, the relative risks for each transition were estimated separately by calculation of hazard ratios (HR) using the Cox Proportional Hazards model, controlled for all covariates. Then, we analyzed the HR of the transitions, stratified by the three calendar time periods (1994-1999, 2000-2005, 2006-2011), still controlling for all covariates. A P-value < 0.05 was considered statistically significant. We present hazard ratios (HR) with 95% confidence intervals, and we corrected the results from the multi-state model for multiple testing using the Benjamini Hochberg correction.[19] SAS version 9.2 was used for statistical analyses.

RESULTS

Population characteristics

At study entry, most patients (74 %) were female, and 74% were 40-59 years of age (table 1). Thirty-one percent of the RA patients had one or more somatic comorbidity, and 9% had one or more psychiatric comorbidity. Age, gender, household status, level of education, physical job exposure and city size were largely similar between patients and controls, whereas more patients than controls were of Danish origin. Compared to the controls, more patients suffered from somatic, but not psychiatric, comorbidities (Table 1).

Table 1. Characteristics of patients and controls when entering the study[7]*

		Rheumatoid arthritis	Controls
		% (N = 6,677)	% (N=56,955)
Year of Diagnosis	1994 - 1999	38.5	-
	2000 - 2005	31.9	-
	2005 - 2011	29.6	-
Gender	Female	73.6	73.3
	Male	26.4	26.7
Age	≤ 29 years	7.5	7.2
	30-39 years	18.7	19.7
	40-49 years	33.1	33.8
	50-59 years	40.8	39.3
Immigrant status	Danish	94.6	87.0
	Immigrant	5.2	12.8
	Descendants	0.3	0.2
Household composition	Cohabitants with or without children	77.4	77.3
	Single, no children	22.6	22.7
City size	Capital centre	14.1	12.6
	Closest suburbs	13.9	15.5
	The metropolitan area	6.5	7.6
	City > 100,000	9.9	12.1
	City 10,000 – 100,000	29.4	27.5
	The rest of the country	26.2	24.8
Highest obtained education	Elementary school/high school	33.7	33.2
	Vocational training	39.6	35.8
	Tertiary/polytechnic school	20.9	22.2
	Higher education (e.g. Master, PhD)	4.2	5.9
	NA	1.6	2.9
Physical job exposure	0	43.3	44.5
Estimated kg lifted per day	1-5999	31.5	32.3
	≥ 6000	25.2	23.2
Somatic Comorbidity	0	69.4	75.7
	≥1	30.6	24.3
Psychiatric Comorbidity	0	91.3	92.2
	≥1	8.7	7.8

*Source: Hansen et al, J Rheumatol 2016 (in press): All rights reserved

Rates of sickness absence, unemployment, return to work and disability pension

For RA patients at work, the rate of long term sickness absence (transition #1) was 359 per 1000 PY in the first year after diagnosis and 151 per 1000 PY in subsequent years (table 2 and figure 1), and notably higher than for controls (80 per 1000 PY for both). The rates of long term sickness absence for unemployed patients (#2) were 206 per 1000 PY in the first year and 103 per 1000 PY in subsequent years, and higher than for controls. The unemployment rates were lower for RA patients than for controls, especially for the transition from long term sickness absence to unemployment (#4), but also for work to unemployment (#3). However, the rates of return to work (#5 and #6) were also lower for RA patients suggesting that their long term sickness absence and unemployment periods were longer relative to controls.

For all comparisons, RA patients had higher rates of disability pension than controls. For both RA patients and controls, the rate of disability pension was highest for persons on long term sickness absence (#8). Few achieved disability pension while unemployed (#9) and even fewer transitioned to disability pension from work (#7). For the patients with RA, the rates of disability pension were lower in the first year after diagnosis than in subsequent years.

Table 2. Events, Person Years (PY), and transitions rates for the Rheumatoid Arthritis sample and for the Control sample

		Rheumatoid Arthritis		Controls	
#	Transitions	< 1 y	≥ 1 y	< 1 y	≥ 1 y
1	Work to Long term sickness absence				
	PY	2735	19,577	30,399	266,270
	Events	983	2951	2417	21,404
	Rate (Events / 1000 PY)	359	151	80	80
2	Unemployment to Long term sickness absence				
	PY	654	4289	6209	51,258
	Events	135	440	481	4253
	Rate (Events / PY)	206	103	77	83
3	Work to unemployment				
	PY	2735	19,577	30,399	266,270
	Events	842	4719	10,056	82,003
	Rate (Events / PY)	308	241	331	308
4	Long term sickness absence to unemployment				
	PY	1289	3776	2179	19,698
	Events	132	515	574	4979
	Rate (Events / PY)	102	136	263	253
5	Long term sickness absence to work				
	PY	1289	3776	2179	19,698
	Events	721	2745	2058	19488
	Rate (Events / PY)	559	727	944	989
6	Unemployment to work				
	PY	654	4289	6209	51,258
	Events	867	4990	10,334	84,876
	Rate (Events / PY)	1326	1163	1664	1656
7	Work to Disability pension				
	PY	2735	19,577	30,399	266,270
	Events	83	720	108	782
	Rate (Events / PY)	30	37	4	3
8	Long term sickness absence to Disability pension				
	PY	1289	3776	2179	19,698
	Events	211	1151	248	2163
	Rate (Events / PY)	164	305	114	110
9	Unemployment to Disability pension				
	PY	654	4289	6209	51,258
	Events	32	257	119	1026
	Rate (Events / PY)	49	60	19	20

Risks of sickness absence, unemployment, return to work and disability pension

In the first year after being diagnosed with RA, patients had approximately 4 times greater risk of long term sickness absence compared to general population controls (HR 4.00), and in subsequent years the HR was 1.84 (table 3).[7] For unemployed RA patients, the HR of long term sickness absence was 2.46 in the first year after diagnosis, decreasing to HR 1.62 in subsequent years.

In the first year after diagnosis, the risk of unemployment was similar in RA patients and in controls (table 3). In subsequent years, the risk of unemployment was lower (HR 0.62) for the RA patients. For RA patients on long term sickness absence the relative risk for unemployment was 0.42 in the first year after diagnosis and 0.62 in subsequent years.

The probability of returning to work from either long term sickness absence or from unemployment was lower for RA patients than for the controls (HR 0.80). This was particularly pronounced for RA patients in the first year after diagnosis (HR 0.60).

For both work, long term sickness absence, and unemployment, the risk for disability pension was significantly increased for RA patients in the first year after diagnosis (HR 8.60, 1.52, and 2.36 respectively) with further increases in the subsequent years (HR 12.20, 2.75, and 3.41, respectively) (table 3).

Table 3. Hazards ratios for the 9 transitions. Rheumatoid arthritis patients compared to matched general population controls during follow up

Transitions			Disease duration < 1 y			Disease duration ≥ 1 y		
#	From	To	HR	P	(CI95%)	HR	P	(CI95%)
1	Work	Long term sickness absence	4.00	***	(3.64-4.30)	1.84	***	(1.75-1.94)
2	Unemployment	Long term sickness absence	2.46	***	(1.99-3.04)	1.62	***	(1.45-1.81)
3	Work	Unemployment	0.92		(0.83-1.03)	0.82	***	(0.77-0.87)
4	Long term sickness absence	Unemployment	0.42	***	(0.35-0.51)	0.62	***	(0.56-0.69)
5	Long term sickness absence	Work	0.60	***	(0.55-0.66)	0.78	***	(0.75-0.82)
6	Unemployment	Work	0.77	***	(0.70-0.85)	0.80	***	(0.76-0.83)
7	Work	Disability pension	8.60	***	(6.34-11.67)	12.20	***	(10.96-13.58)
8	Long term sickness absence	Disability pension	1.52	***	(1.26-1.84)	2.75	***	(2.54-2.98)
9	Unemployment	Disability pension	2.36	***	(1.57-3.54)	3.41	***	(2.92-3.98)

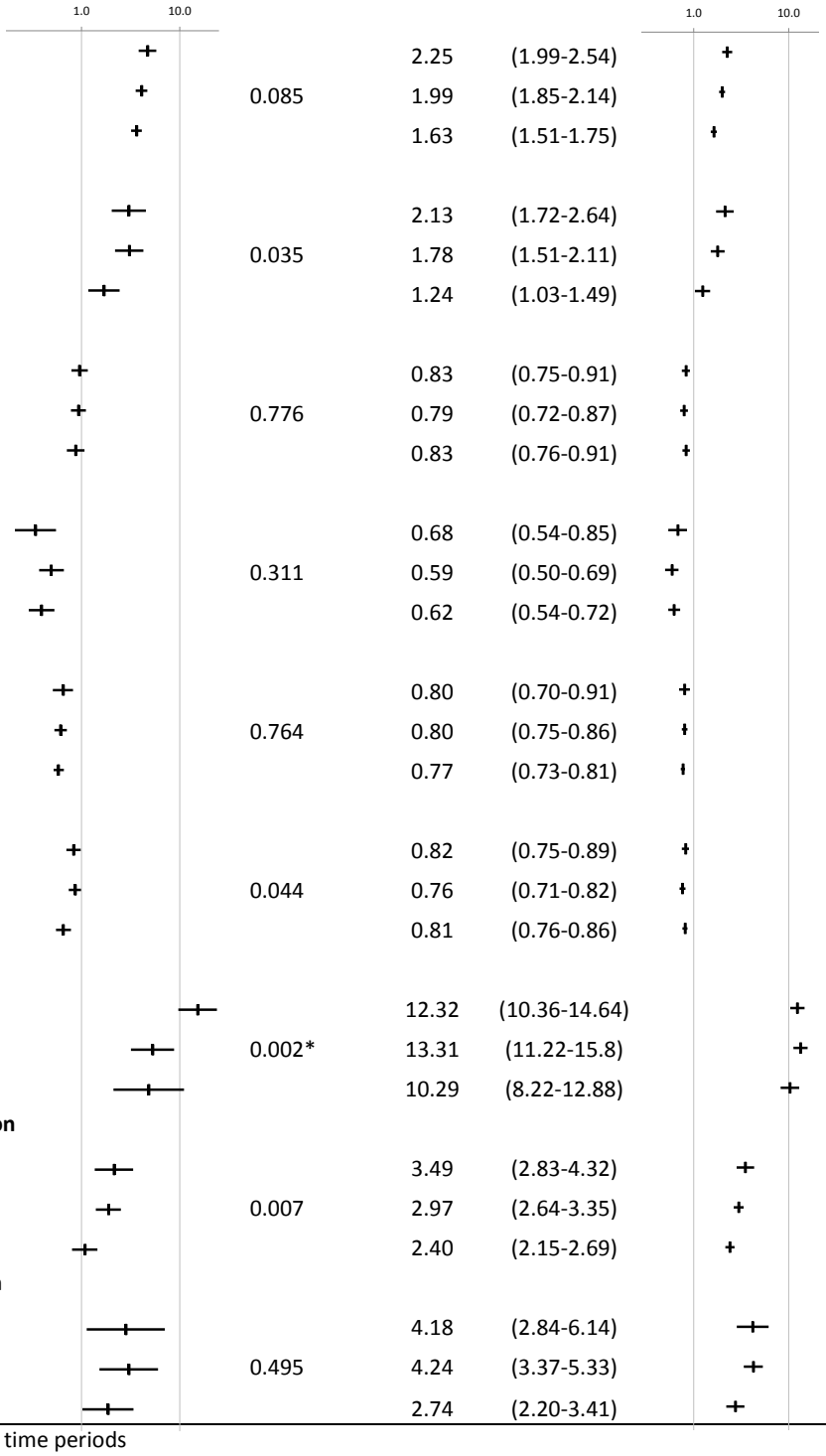
Numbers (1)…(9) correspond to transitions in figure 1, * P < 0.5 ** P < 0.01 *** P < 0.001

Changes in risk from 1994 to 2011

In table 4 the HR were stratified according to the year of diagnosis (1994-1999, 2000-2005, and 2006-2011). Overall, results showed a reduction in the HR of long term sickness absence from 1994-1999 to 2006-2011, which was highly significant in patients at work with more than 1 year's disease duration (HR decreasing from 2.25 to 1.63), but no reduction was observed in patients with <1 year's disease duration. No significant changes over time were seen in the HR of unemployment or for the HR of return to work. For disability pension, a trend towards lower HRs was seen for all comparisons and the decrease was statistically significant for the transition from work to disability pension in the first year after diagnosis (HR decreasing from 15.17 to 4.83). The risk of disability pension in the subsequent years after diagnosis did not change for patients working during the period (HR>10). The risk of disability pension after long term sickness absence decreased significantly over time, but remained high in patients with more than 1 year's disease duration (HR decreasing from 3.49 to 2.40).

Table 4. Hazard rates for the 9 transitions for rheumatoid arthritis patients diagnosed in three different time intervals

	Disease duration < 1 y			Disease duration ≥ 1 y		
	HR	(95% CL)	P[a]	HR	(95% CL)	P[a]
1. Work to Sickness absence						
1994 – 1999	4.69	(3.82-5.76)		2.25	(1.99-2.54)	
2000 – 2005	4.08	(3.56-4.67)	0.085	1.99	(1.85-2.14)	0.000*
2006 – 2011	3.63	(3.20-4.11)		1.63	(1.51-1.75)	
2. Unemployment to Sickness absence						
1994 – 1999	3.03	(2.03-4.52)		2.13	(1.72-2.64)	
2000 – 2005	3.06	(2.19-4.26)	0.035	1.78	(1.51-2.11)	0.004*
2006 – 2011	1.69	(1.17-2.44)		1.24	(1.03-1.49)	
3. Work to Unemployment						
1994 – 1999	0.95	(0.79-1.16)		0.83	(0.75-0.91)	
2000 – 2005	0.93	(0.78-1.11)	0.776	0.79	(0.72-0.87)	0.669
2006 – 2011	0.87	(0.71-1.07)		0.83	(0.76-0.91)	
4. Sickness absence to Unemployment						
1994 – 1999	0.34	(0.21-0.55)		0.68	(0.54-0.85)	
2000 – 2005	0.49	(0.37-0.66)	0.311	0.59	(0.50-0.69)	0.705
2006 – 2011	0.39	(0.29-0.53)		0.62	(0.54-0.72)	
5. Sickness absence to Work						
1994 – 1999	0.65	(0.51-0.82)		0.80	(0.70-0.91)	
2000 – 2005	0.61	(0.53-0.71)	0.764	0.80	(0.75-0.86)	0.664
2006 – 2011	0.58	(0.52-0.66)		0.77	(0.73-0.81)	
6. Unemployment to Work						
1994 – 1999	0.83	(0.70-0.98)		0.82	(0.75-0.89)	
2000 – 2005	0.86	(0.74-0.99)	0.044	0.76	(0.71-0.82)	0.249
2006 – 2011	0.65	(0.55-0.78)		0.81	(0.76-0.86)	
7. Work to Disability pension						
1994 – 1999	15.17	(9.65-23.86)		12.32	(10.36-14.64)	
2000 – 2005	5.28	(3.18-8.76)	0.002*	13.31	(11.22-15.8)	0.186
2006 – 2011	4.83	(2.11-11.05)		10.29	(8.22-12.88)	
8. Sickness absence to Disability pension						
1994 – 1999	2.14	(1.36-3.35)		3.49	(2.83-4.32)	
2000 – 2005	1.88	(1.40-2.51)	0.007	2.97	(2.64-3.35)	0.004*
2006 – 2011	1.08	(0.80-1.45)		2.40	(2.15-2.69)	
9. Unemployment to Disability pension						
1994 – 1999	2.82	(1.13-7.03)		4.18	(2.84-6.14)	
2000 – 2005	3.03	(1.52-6.01)	0.495	4.24	(3.37-5.33)	0.009
2006 – 2011	1.86	(1.02-3.38)		2.74	(2.20-3.41)	



[a] Test of equal hazard rates across the 3 time periods

* significant when corrected for multiple testing, Benjamini Hochberg

DISCUSSION

Patients with rheumatoid arthritis are at high risk of long term sickness absence and disability pension.[7, 9, 10] The main findings of the present study were that although the risk of long term sickness absence and disability pension decreased since 1994 compared to the general population, the risk remained high, both in early and more established disease. Furthermore, we report that RA patients were less likely to return to work after long term sickness absence or unemployment, and this risk had *not* improved during the last two decades.

Our results showed that RA patients, compared to the general population, had higher rate and HR of long term sickness absence, especially in the first year after diagnosis, but also in subsequent years. This is in line with other studies, that showed a dramatic increase in mean days of long term sickness absence in the time right after diagnosis.[9, 10] We extended these findings even further by showing that this applied both to patients who were at work and patients who were unemployed prior to the long term sickness absence.

The availability of high-quality national registers in Denmark enabled us to perform extensive, multi-state analyses with a large patient population. The multi-state analysis took all actual work shifts and states in each individual into account, and also adjusted for the corresponding risks in the general population, thereby isolating the impact of RA per se on all outcomes (long-term sickness absence, unemployment, disability pension and return to work). The results of our comprehensive analyses expand previous findings in two descriptive studies, which reported a decrease in mean days of long term sickness absence per year in established RA between 1995 and 2010 counteracted by an increase in mean days of disability pension per year.[9, 20]

Another study showed in a simple trend test based on mean square successive differences, without adjusting for multiple testing, a decrease in sick leave for RA patients and an increase in employed

RA patients simultaneously.[6] We found that the relative risk of long term sickness absence and from long term sickness absence to disability pension decreased significantly from 1994 to 2011 in patients with more established disease (≥1 year since diagnosis). Due to the study design this decrease can be attributed to the RA diagnosis per se, i.e. it is not due to societal changes. It may, at least in part, be associated with altered treatment strategies, e.g. early and aggressive use of synthetic and biologic DMARDS. However, since the risk remains much higher than in the background population, there is an unmet need of initiatives that may help to retain patients with RA in the working force.

In our study, the rates and risks of unemployment for RA patients were similar to or lower than for the general population both in early and more established disease. However, it should be noted that the DREAM register does not distinguish between a sick-listed employee and a sick-listed unemployed person until the sick-listed person reports him or herself unemployed. It is possible that losing a job prolongs the sickness absence period and delays return to work.[2] This may have been of relevance for persons in the age range 50-59 years, who may have chosen to wait for early retirement (possible from the age of 60 years) instead of applying for disability pension.[2] This may in particular have affected the RA patients, since 40% of our population were in this age group at study entry. Hence, our study may have underestimated the risk of unemployment from long term sickness absence, but we do not know the frequency of such events.

The chance of returning to work from sickness absence was markedly reduced for RA patients relative to controls on long term sickness absence from the general population, especially in the first year after diagnosis. This may, at least in part, be explained by the registration bias mentioned above. Also, the chance of returning to work from unemployment was significantly lower compared to unemployed controls, both in the first year after diagnosis and in the subsequent years. This significant impact of RA on the chances of returning to work was unchanged during the study

period and thus did not appear to be affected by modern treatment strategies. To our knowledge, this outcome has not been investigated previously.

Our results showed that the most common trajectory to disability pension was from long term sickness absence, for both RA patients and controls, and the relative risk for RA patients was high. The relative risk of shifting to disability pension from work was even higher, and the risk was also markedly increased for unemployed patients. Modern treatment strategies and other changes in the handling of RA have had a positive impact on the risk of disability pension from work in the first year after diagnosis and for long term sickness absence in the subsequent years. Still, the risk of disability pension in patients with RA of more than one year's duration remain at least 2.5 times increased compared to the general population.

The present study was a large cohort study with up to 17 years' follow up. Our population was retrieved from the nationwide, high quality, and highly validated databases DANBIO and DREAM. The majority of patients in our study were ethnic Danish women between 40 and 59 years of age. One third of them had one or several somatic comorbidities at study entry. The control group was matched on age, gender and residence area, and except for minor differences regarding ethnicity and the incidence of somatic comorbidity, the two groups were largely similar. This provided us with a sound basis to estimate the impact of RA on the risk of sickness absence, unemployment and of disability pension, respectively, and also to study the chances of returning to work after a period of sickness or unemployment. Our analyses included all the shifts made throughout the study period, so all results were relative to each other, and controlled for all covariates.

A limitation of our study is that the Danish registers do not collect data on sick leave shorter than 3 weeks. Thus, we were not able to estimate the total number of sick days for each patient. The results may also have been influenced by selection bias in the patient population, because our follow up

period starts in 1994, whereas DANBIO was founded in the year 2000. This means, that if there were RA patients between 18 and 59 years of age, who died before year 2000, they were not registered in DANBIO and only included in our study, if they were registered in NPR and identified among the controls. Such patients would be expected to have severe illness, and thus, our risk estimates for the period 1994-1999, and the decrease in HR from 1994-1999 to 2006-2011 may have been underestimated.[7]

In conclusion, RA patients remain at high risk for sickness absence and disability pension despite a positive trend between 1994 and 2011. Further improvements are likely to occur, if modern treatment strategies succeed in preventing chronic physical disability for RA patients. From the patient's and the rheumatologist's perspective, an important rehabilitation challenge is to improve the probability of returning to work for RA patients that are on long term sick leave or unemployed.

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COMPETING INTERESTS

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The other authors declared no competing interests.

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ETHICS APPROVAL

The study was approved by The Danish Data Protection Agency, journal number: 2015-41-3828.

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Paper III:

Work Environmental Risk Factors for Long Term Sickness Absence in Patients with Rheumatoid Arthritis - A Two Year Prospective Cohort Study

Submitted

Work Environmental Risk Factors for Long Term Sickness Absence in Patients with Rheumatoid Arthritis - A Two Year Prospective Cohort Study

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Abstract

Aim

To identify work environment risk factors for long term sickness absence (LTSA) among patients with rheumatoid arthritis (RA).

Methods

A two year follow-up study of 895 patients with RA, who were working. Respondents evaluated their work environment at baseline using standard occupational health questionnaires and rated their health and functioning using the SF-36v2 health survey. Sociodemographic data was collected through public registers and compared with a general population sample. Data on LTSA in the two years after baseline was collected through public registers. The risk of LTSA was analysed using proportional Hazards models.

Results

Compared with the general population, more employed RA patients had high education and jobs doing "knowledge work". After control for sociographic variables and physical function, three work environment variables significantly predicted LTSA: Physical demands at work was a major risk factor for LTSA (HR=4.944(CL:1.358-18.001)), while "degree of freedom at work" and "leadership quality" were protective factors. No significant associations were found for 5 other work environment factors (working in a cold environment, emotional demands, influence, social support from supervisors, social responsibility at work).

Conclusion

Risk of LTSA was increased for RA patients with high physical job demands and decreased for RA patients with high degrees of freedom at work and high leadership quality. We found indications that selection into job with less physical strain had already taken place, suggesting that our data may underestimate the true effect of work environment factors for RA patients.

Introduction

Rheumatoid arthritis (RA) is the most common inflammatory rheumatic disease[1]. Disease onset may occur at any age, but the incidence peaks in the fourth and fifth decade of life. RA has large impact on the patient's physical function and somatic and mental health, which makes long term sickness absence (LTSA) an important outcome, both from an individual and a societal perspective. For the individual, LTSA often leads to reduced income and loss of contact with colleagues. Further, the individual has higher risk for permanent exclusion from the labor market. From a societal perspective, LTSA represents a significant loss of production and is a substantial economic burden[2;3;4]. Previous studies of employment in RA patients have found increased risk for LTSA in RA patients compared to the general population[5-8]. The risk of LTSA appears to be reduced by modern treatment strategies [9;10], such as earlier and more aggressive treatment, combined with synthetic and biologic disease-modifying anti-rheumatic drugs (DMARDs)[11-14]. LTSA and job loss risk is influenced by RA severity and duration and previous studies have focused on these factors[7;11;15;16]. However, risk of LTSA may also be influenced by personal and environmental factors such as gender, age, lifestyle, physical and mental job demands, educational level, and socio-economic status[11;17;18]. Better knowledge of such risk factors is important for a comprehensive effort to maintain work ability and reduce the risk of LTSA for RA patients.

One previous study has examined work environment factors and sick leave for patients with early inflammatory rheumatic disease (n=210) of whom 23% had RA. This cross-sectional study found that low control over ones job was associated with LTSA (Odds Ratio [OR] 2.74). Other risk factors were poor physical functioning, pain, and passive behavioural coping [19].

The aim of this study was to evaluate the association of work environment factors and LTSA in a prospective analysis of a large RA population. Work related risk factors were assessed through self-report questionnaires at baseline, while LTSA was registered through administrative

databases during a two years' follow-up period (2011-2013).

Methods

Data sources

We identified patients with RA in the nationwide DANBIO registry, which monitors patients with inflammatory arthritis[20]. Individual data on LTSA was obtained from the DREAM register, which provides weekly information on social transfer payments for all residents in Denmark. DREAM has been shown to be suitable for follow-up of social consequences of disease[2;21]. Information on age, gender, job type, ethnicity, highest obtained education, and type of cohabitation were obtained from registries in Statistics Denmark. Data from all the registers used were linked through the central personal register number, a unique personal identifier given at birth to all Danes.

Ethics approval

The study was registered and approved by the Danish Data Protection Agency, identification number: 2015-41-3828.

Population

Figure 1 illustrates the selection of the study population of RA patients. DANBIO was screened for RA patients eligible for this study. A total of 5,124 patients with RA aged 18-64 years at 25th of March 2011 were identified in the DANBIO registry. The patient population was merged with the DREAM database, and patients on early retirement, on disability pension, not resident in Denmark, on welfare, patients who had died or patients who registered as not willing to participate in research via their cpr number were excluded. The population was limited to patients aged 18-59 years at May 1st 2010. The final RA population to receive questionnaire consisted of 2,013 patients. The questionnaire was sent on May 3rd 2011. In case of non-response, reminders were sent after 2 and 4 weeks. After 5 weeks, Statistics Denmark contacted all non-responders by phone. A total of 1,735

(87%) RA patients answered the questionnaire, of which 1,728 could also be found in the registers in Statistics Denmark. The following respondents were excluded: RA patients who had been working when included in the analysis, but who was on LTSA (n = 120) or disability pension (n = 428) at the time of answering the questionnaire. Persons working on special terms, or receiving early retirement pension were all classified as receiving disability pension and excluded (N=428). Patients who were students, emigrants, or on leave during the entire 2 year follow up period (n = 8) were also excluded, as were those who had missing values on one or more items relevant for the analyses in this study (n=277). Thus, the final study population comprised 895 working patients with RA aged 18-59 years. A general population comparison sample - matched on gender and age - was identified in Statistics Denmark (1:10) to form a comparison group for distribution on background variables. Patients were followed up in DREAM and follow-up ended at June 30th 2013.

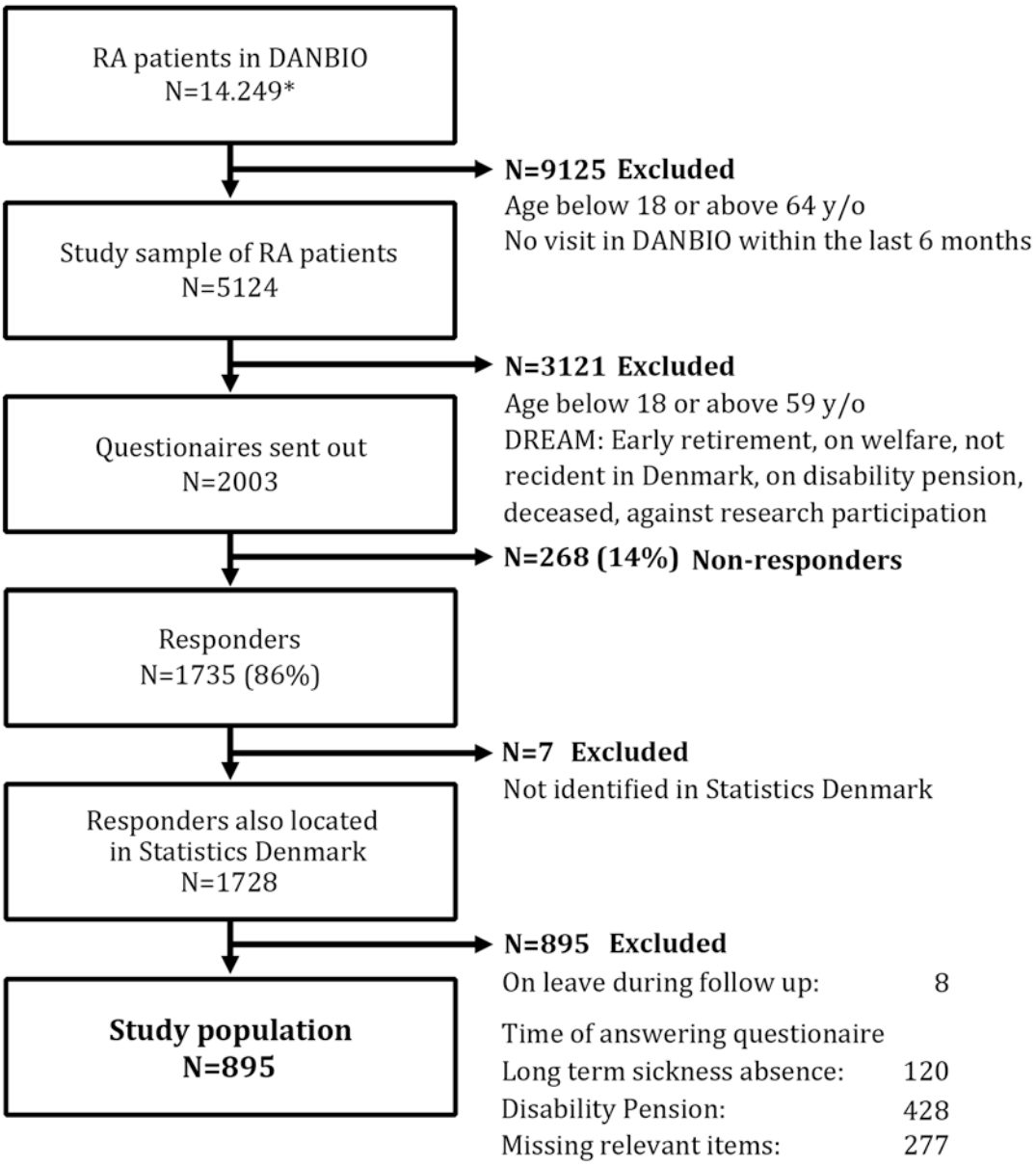

Figure 1, Patient disposition over inclusion and exclusion criteria defining the study population of RA patients in study 3/cohort B.
*By 31st of December 2013[32]

Primary outcome

The primary outcome was LTSA, defined as being sick listed in DREAM. Individuals were classified as being on LTSA if receiving sickness absence benefits for a period of 4 weeks or more. The period of 4 weeks was chosen, since this was the time (at the time of this study) where Danish municipalities became responsible for sickness absence compensation, leading to very high completeness of case registration in DREAM.

Test of the questionnaire in interviews

The questionnaire used items from well-established surveys. Pre-testing with 21 RA patients recruited through the outpatient rheumatology clinic at Rigshospitalet (former: Glostrup Hospital) evaluated whether: 1) the questionnaire covered all relevant issues for RA patients; 2) irrelevant questions were present; and 3) the questions could be understood and answered by RA patients. The respondents included 14 women and 7 men. All respondents were employed and between 18 and 64 years of age, except one man of 74 years (interviewed about self-efficacy question), and one unemployed woman (interviewed about the health questions). The choice and wording of the questions were evaluated and revised during the interview process, until new interviews did not reveal further issues in the questionnaire. *Physical function* was assessed by using the 10 items scale from the SF-36v2[22] (table 1). The answers were scored on a scale from 0 (worst) to 1 (best function). *The physical working environment* was assessed using items from the Danish Work Environment Cohort Study[23] (DWECS), which were scored as two scales: *physical demands at work* (9 items), and *exposure to cold or draught* (2 items) on a scale from 0 (low demands/exposure) to 1 (high demands/exposure). We measured six psychosocial work characteristics from Copenhagen Psychosocial Questionnaire[24] (COPSOQ): *Emotional demands* (1

item), *influence at work* (5 items), *degrees of freedom* (3 items), *support from supervisors* (3 items), *quality of leadership* (6 items of which 3 came from the DWECS study), and *corporate social responsibility* (1 item - Table 1). Scales were scored from 0 to 1, with 0 indicating least of the characteristic in question and 1 indicating highest level of influence, emotional demands, degree of freedom, support, quality of leadership and social responsibility.

Table 1. Wording of questions on physical function and the working environment

Physical function	
Does your health now limit you in:	*vigorous activities*[1] *moderate activities*[1] *lifting or carrying groceries*[1] *climbing several flights of stairs*[1] *climbing one flight of stairs*[1] *bending kneeling or stooping*[1] *walking more than a mile*[1] *walking several block*[1] *walking one block*[1] *bathing or dressing*[1]
Physical demands at work	
How much of your time at work are you…	*standing in the same spot,*[2] *working with arms lifted* [2] *bending or twisting in the back or neck* [2] *doing repetitive movements* [2] *kneeling* [2] *squatting* [2] *pushing*[2] *pulling*[2]
Exposure to cold or draught	
How much of your time at work are you…	*Subjected to the cold(Work outside in the winter, in chilly rooms, e.c.t.)*[2] *Subjected to a draft (air current)?*[2]
Influence at work	
Do you have a large degree of influence concerning your work?[3]	
Can you influence the amount of work assigned to you?[3]	
Do you have any influence on what you do at work? [3]	
Do you have a say in choosing who you work with? [3]	
Do you have any influence on your work schedule? [3]	
Emotional demands	
Do you have to relate to other people's personal problems as part of your work? [3]	
Degrees of freedom	
Can you decide when to take a break? [3]	
Can you leave your work to have a chat with a colleague? [3]	
If you have some private business, is it possible for you to leave your place of work for half an hour without special permission? [3]	
Support from supervisor	
How often is your nearest superior willing to listen to your problems at work?[4]	
How often do you get help and support from your nearest superior? [4]	
How often does your nearest superior talk with you about how well you carry out your work? [4]	

Table 1. Wording of questions on physical function and the working environment

Quality of leadership	
To what extent would you say that your immediate superior:	*makes sure that the individual member of staff has good development opportunities?*[5]
	gives high priority to job satisfaction?[5]
	is good at work planning?,[5]
To what extent does the management	*communicate a clear and positive vision for the future?*[5]
	encourage the employees to view the problems in a new way?[5]
	clearly express their values and live by them?[5]
Corporate social responsibility	
Is there space for employees with various illnesses or disabilities?[6]	

[1] Response categories: *"Yes, limited a lot, Yes, limited a little, No, not at all"*.
[2] Response categories: *Almost all the time, Approximately 3/4 of the time, Approximately 1/2 of the time, Approximately 1/4 of the time, Rarely/very little, Never"*.
[3] Response categories: *"Always, Often, Sometimes, Rarely, Never/Almost never"*.
[4] Response categories: *"Always, Often, Sometimes, Rarely, Never/Almost never, Not relevant"*.
[5] Response categories: *"To a very high degree, To a high degree, To some degree, To a slight degree, To a very slight degree, Not relevant"*.
[6] Response categories: *"To a very high degree, To a high degree, To some degree, To a slight degree, To a very slight degree"*.

Information on the covariates was identified via the central population register (CPR register) at Statistics Denmark: Gender, age, immigrant status,cohabitation, highest obtained education, and job type. The DREAM register was used to identify LTSA or unemployment in the 30 days before answering the questionnaire.

Statistical analysis

The effect of the self-reported factors from the questionnaire on LTSA was analyzed using the Cox Proportional Hazards model for repeated events with a random person effect (frailty model) [25;26]. The underlying time variable was time since answering the questionnaire (Figure 2). Patients entered the analysis when answering the questionnaire (late entry) and were followed until LSTA, censoring, or temporarily out of risk. Subjects were censored if they died, turned 60 years, or received disability pension before the end of the observation period (i.e. two years after study entry). Subjects were temporarily out of risk if they were on maternity leave or other kinds of leave, if they emigrated or became students. Subjects who became unemployed during follow-up were

kept in the analysis, since LTSA is also registered for the unemployed. Each work environment variable was included as an independent variable in the "crude" analyses (without control for covariates) and in adjusted analyses (controlled for covariates and physical functioning). All covariates except gender and immigrant status were treated as time-dependent variables, thus taking into account that individuals may change status during the period of observation

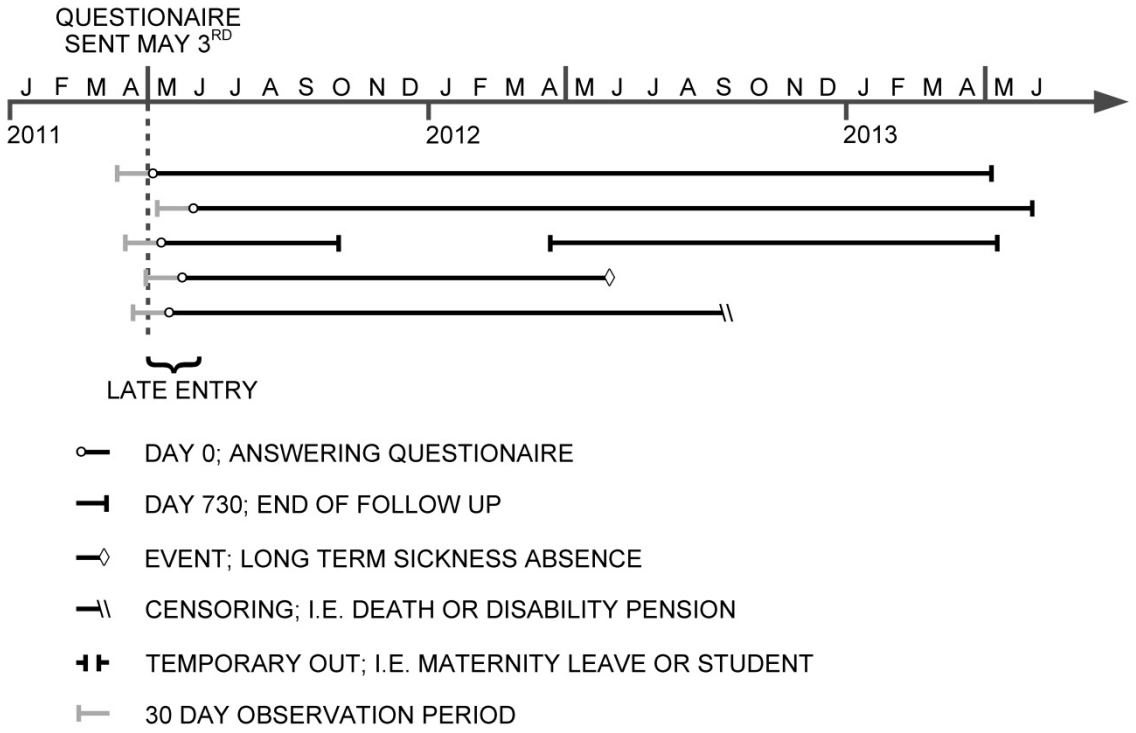

Figure 2, Cox proportional hazards model with late entry. At day 0 the questionnaire was answered and the patient with rheumatoid arthritis (RA) entered the analysis. Thus day 0 depended on the answering date, and so did end of follow up, which was 2 years after answering (day 730). If an RA patient had long term sickness absence (the event), or was censored, the patient was out of risk and left the analysis. If the RA patient was on leave or became a student, the RA patient was temporary out of risk, and entered the analysis again when they returned to work or unemployment afterwards (frailty model).

The analysis was done using the PHREG statement in SAS version 9.2. The assumption of proportional hazards was investigated by visual inspection of cumulative hazard curves for each independent variable.

Results

Table 2 describes the characteristics of the RA study population when entering the study, compared to the general population. More RA patients were ethnic Danes (96.4%), living in a relationship (80.0%), had at least a bachelor's degree (79.7%), and were knowledge workers (43.6%). Few RA patients had experienced LTSA (0.9%) or unemployment (3.4%) during the 30 days preceding baseline.

Table 2. Characteristics of the RA sample compared to matched controls

Co-variates		% RA population (n = 895)	% Control population (n = 8949)
Gender	Male	25.6	25.6
	Female	74.4	74.4
Age groups	18-29	3.0	2.6
	30-39	14.5	13.1
	40-49	32.9	30.0
	50-59	49.6	54.4
Ethnicity	Danish	96.4	84.2
	Immigrant	3.6	13.1
	Not available	0	2.7
Family Type	Couple	80.0	75.3
	Single	20.0	22.0
	Not available	0	2.7
Highest obtained education	Higher education (e.g. Master, PhD)	9.7	8.6
	Tertiary/polytechnic school (e.g. Bachelor's degree)	31.5	26.6
	Technical and vocational education and training[a]	41.7	36.4
	Secondary school/sixth form school	16.1	23.3
	Not available	1.0	5.1
Job type	Management	3.9	3.0
	Knowledge workers I (e.g. professors, lawyers, engineers)[b]	27.4	20.2
	Knowledge workers II (e.g. technicians and associate professionals)[c]	16.2	10.6
	Clerical support work	9.4	8.05
	Sales, service and care	13.5	13.7

Table 2. Characteristics of the RA sample compared to matched controls

	Work with high physical load[a]	10.3	14.3
	Not available	19.3	30.3
Long term sick leave within previous 30 days	No	99.2	-
	Yes	0.8	-
Unemployment within previous 30 days	No	96.7	-
	Yes	3.4	-

[a] Prepares people for specific trades, crafts and careers at various levels from a trade, a craft, technician, or a high professional practitioner position in careers such as engineering, accountancy, nursing, medicine, architecture, law etc.
[b] Science, engineering, medical science, education, economy, law
[c] Technicians in transport and aviation, health care, in trade, finance, administration, law, sports, religion
[d] Military, farming, gardener, forestry, hunting, fishing, craft, machine operator, drivers, construction workers, routine manual work

Table 3 presents the hazard ratios for the covariates. Age, gender, family type, education, and previous unemployment were not significant predictors of LTSA, Previous LTSA was a strong risk factor for LTSA, while good physical function was strongly associated with low risk. Also, lower risk of LTSA was observed for knowledge workers type II (e.g. technicians) and for immigrants (as compared to ethnic Danes).

Table 3. Hazard ration of long term sickness absence for rheumatoid arthritis patients according to basic co-variates and physical functioning

Parameter	Class	HR	95 % CL	P*
Age	18-29 years	2.667	(0.978-7.275)	0.210
	30-39 years	1		
	40-49 years	1.026	(0.548-1.919)	
	50-59 years	1.145	(0.644-2.036)	
Gender	Female	1		0.668
	Male	0.910	(0.592-1.399)	
Ethnicity	Danish	1		
	Immigrant	0.094	(0.011-0.772)	
Family type	Couple	1		0.469
	Single	0.848	(0.544-1.323)	
Highest obtained education	Higher education (e.g. Master. PhD)	0.971	(0.407-2.316)	0.586
	Tertiary/polytechnic school (e.g. Bachelor's degree)	1.381	(0.763-2.498)	
	Technical and vocational education and training*	1.064	(0.630-1.795)	
	Secondary school/sixth form school	1		

	Not available	2.159	(0.455-10.245)	
Job type	Management	1.062	(0.303-3.724)	**0.022**
	Knowledge workers I (e.g. professors. lawyers. engineers)[c]	1.659	(0.857-3.212)	
	Knowledge workers II (e.g. technicians and associate professionals)[d]	1		
	Clerical support work	1.657	(0.704-3.900)	
	Sales. service and care	2.739	(1.348-5.567)	
	Work with high physical load[e]	1.492	(0.620-3.595)	
	Not available	2.840	(1.441-5.598)	
Previous long term	No	1		**<.000**
sickness absence[a]	Yes	4.389	(2.263-8.512)	
Previous unemployment[a]	No	1		0.675
	Yes	0.822	(0.329-2.054)	
Physical functioning[b]		0.101	(0.046-0.218)	**<.000**

* General test of association

[a] in the last 30 days before answering the questionnaire and entering the analysis

[b]Physical Functioning Scale, 10 items from SF-36 version 2, entered in the analysis as a linear variable

[c]i, e, science, engineering, medical science, education, economy, law

[d] technicians in transport and aviation, health care, in trade, finance, administration, law, sports, religion

[e]i, e, military, farming, forestry, fishing, craft, machine operator, drivers, construction workers, routine manual work, other kinds of manual work

Table 4 presents results for the association of each work environment variable and LTSA in unadjusted and adjusted analyses (controlling for ethnicity, job type, previous LTSA and physical function). The risks of LTSA was significantly increased for RA patients with high physical job demands and significantly lower for patients having high degrees of freedom at work and for patients working under a leadership they rated highly. The latter two associations were weakened slightly when controlling for covariates, but remained significant at a 5% level. Non-significant associations were found for working in a cold environment, emotional demands at work, influence at work, social support from supervisors, and social responsibility at work.

Table 4. Hazard ratios of long term sickness absence according to working environment variables with and without control for covariates. Rheumatoid arthritis patients (n= 895)

	Raw effect			Controlled effect*		
Working environment variables	HR	95% CL	P	HR	95% CL	P
Physical demands at work	**4.312**	**(1.337-13.905)**	**0.014**	**4.944**	**(1.358-18.001)**	**0.015**
Cold working environment	1.650	(0.870-2.398)	0.184	1.405	(0.647-3.054)	0.390
Emotional demands at work	1.445	(0.788-3.455)	0.155	1.318	(0.782-2.222)	0.300
Influence at work	0.625	(0.328-1.193)	0.154	0.584	(0.297-1.148)	0.119
Degrees of freedom at work	**0.414**	**(0.222-0.775)**	**0.006**	**0.515**	**(0.271 -0.979)**	**0.043**
Social support from supervisors	0.574	(0.286-1.151)	0.118	0.673	(0.328-1.381)	0.281
Quality of leadership	**0.392**	**(0.181-0.848)**	**0.017**	**0.430**	**(0.195-0.950)**	**0.037**
Social responsibility at work	0.514	(0.261-1.012)	0.054	0.610	(0.293-1.272)	0.188

*ethnicity, job type, physical functioning, and previous long term sickness absence

DISCUSSION

Historically, it is well known that RA patients are at high risk for LTSA and early retirement[5-7;11;14;15;27]. Despite more aggressive and effective treatment regimens during the last decades, and an observed decline in risk of LTSA and early retirement, RA patients are likely to continue to be at increased risk also in the future[5-7;11;14;15;27]. Therefore, it is important to identify potential risk factors at the workplace, which might be modified and thereby reducing these risks. Very little research has been done in this field within RA. Thus, a previous cross-sectional, quantitative study of 210 employees found an increased risk of sick leave for patients with low control over their job [19]. Also, passive coping behaviour was associated with increased sick leave, as were indicators for disease severity such a pain and reduced physical function [19]. Studies using qualitative interviews found that suitable working conditions, influence and especially support and positive attitudes from leader and from colleagues were important for maintaining the workability of RA patients[28;29].

Our study addressed physical and psychosocial work environment risk factors for LTSA in a large population of RA patients using a prospective design. We found a strongly increased risk of LTSA for patients with high physical job demands and a reduced risk for RA patients with high degrees of freedom at work and high ratings of quality of leadership. These effects were robust even after controlling for covariates with significant association with LTSA among RA patients: previous LTSA, physical functioning, ethnicity and job type. Thus, while our results are generally in agreement with the few previous studies of RA patients, some nuances are added. Thus, while physical demands at work were a strong risk factor, emotional demands were *not* a significant risk factor for LTSA. Also, degrees of freedom – such as flexibility in taking breaks – seemed more important than influence over work in general. Finally, quality of leadership seemed more important than experienced social support. It may be speculated that in quantitative studies social support is best assessed as the *opportunity for social support* (for which quality of

leadership may be seen as a proxy) rather than *experienced social support*, because the latter is invariably confounded with the need for support.

To a large extent, our results also concur with results for the general population. The association between physical job demands and LTSA is well established[30]. Also, studies have found that "poor quality of leadership" increased the risk of LTSA for female employees [31]. However, LTSA risk factors for men in the general population were "high emotional demands" and demands for "hiding emotions"[31]. Such results were not found in our study of patients with RA.

Among the strengths of the current study is the large sample size, the prospective design, the use of public registers with high coverage, the high questionnaire response rate, and the inclusion of a general population comparison group. This allowed us to evaluate whether "healthy worker" selection effects were present for the RA group. Indeed, results suggested that selection had already taken place. Of 1,728 RA patients of working age (18-59 years), 548 were excluded from the analyses, because they received disability pension, worked protected jobs, or were already on sickness absence. More of the remaining RA patients had high education and worked in jobs with less physical exposure. Thus, RA patients with short education, and/or working in physically strenuous jobs may already have been excluded from the labour marked or switched to less strenuous jobs. Such an effect would lead to an underestimation of the association between risk factors and LTSA.

Another limitation of our study is the lack of an independent assessment of disease severity. We aimed to diminish this problem by including self-assessed physical function as a covariate. Controlling for physical function resulted in a slightly larger estimate for the association between physical job exposures and LTSA. This again suggests that RA patients with more severe disease may have switched to less strenuous jobs.

Self-report of work environment risk factors can be affected by report bias. For

example, self-report of physical job demands has been shown to have large individual variation, because it may be very different from employee to employee how hard they think a given work task is, even if exactly the same physical work is carried out. It is possible that a patient with painful joints may be more aware of the length of time spent kneeling, pushing, or pulling leading to a higher rating of physical job demands than a patient with similar demands but in less pain. Such an effect could lead us to overestimate the effect of the work environment. Considering all the potential sources of bias, we find it more likely that our study has underestimated than overestimated the associations between work environment risk factors and LTSA.

In conclusion, RA patients with physically demanding jobs had higher risk of LTSA compared to RA patients with less strenuous physical jobs. RA patients that reported high degrees of freedom in work or high quality of their nearest leader experienced significantly lower levels of LTSA. These factors should be taken into account when designing interventions to reduce LTSA among RA patients.

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Questionnaire:

“Arbejdsmiljøet for beskæftigede med RA”

Navn:
Adresse:

Arbejdsmiljøet for beskæftigede med leddegigt

DET NATIONALE FORSKNINGSCENTER FOR ARBEJDSMILJØ

DANBIO 4.0
DANSK REUMATOLOGISK DATABASE

VEJLEDNING

Sådan gør du:
Dette spørgeskema handler om dit helbred og dine arbejdsforhold. Hvis du ikke har været i arbejde for nylig, skal du kun udfylde den første halvdel af skemaet.

Det tager ca. 15 - 30 minutter at udfylde skemaet. Det er vigtigt at du så vidt muligt svarer på alle spørgsmålene. De fleste spørgsmål svarer du på ved at sætte et kryds. Ved nogle spørgsmål skal du skrive et tal eller ganske få ord.

Du skal ikke bruge for lang tid på spørgsmålene, men svare det, der først falder dig ind - der er ingen rigtige eller forkerte svar!

Vi behandler din besvarelse strengt fortroligt.

Eksempel på talbesvarelse

2. Hvilket år er du født?

År 1970

Eksempel på afkrydsning

22. De følgende spørgsmål handler om tilrettelæggelsen af dine arbejdstider.
(Sæt ét kryds i hver linie)

Hvor ofte...	Stort set aldrig	Sjældent	Af og til	Ofte	Stort set altid	
1. bliver du bedt om at arbejde på fridage?	☐ 1	☒ 2	☒ 3	☐ 4	☐ 5	Rettet afkrydsning
2. arbejder du mere end 12 timer i træk?	☐ 1	☐ 2	☐ 3	☒ 4	☐ 5	Korrekt afkrydsning

Kommer du til at sætte kryds i en forkert boks, så streg hele boksen ud og sæt krydset i den rigtige boks

Du er velkommen til at ringe eller skrive, hvis du er i tvivl om noget med skemaet eller med undersøgelsen i det hele taget. Vi håber, at du vil deltage i undersøgelsen og glæder os til at modtage din besvarelse.

Med venlig hilsen
Sofie Mandrup Hansen og Merete Lund Hetland

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Tlf. 39 16 54 62
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2100 København Ø
www.arbejdsmiljoforskning.dk

Merete Lund Hetland
Overlæge Reumatologisk Afd.,
Glostrup Hospital

Dato og tilbagemelding

1. Dato.
Skriv venligst hvornår du udfylder spørgeskemaet 2011

Dato Måned År

2. Tilbagemelding.
Er du interesseret i at se, hvordan dine svar på udvalgte spørgsmål ligger i forhold til svarene fra danskere generelt? Hvis ja, så sender vi en helbreds- og arbejdsmiljøprofil til dig .....

Ja	Nej
☐	☐

Spørgsmål om dit helbred

	Fremragende	Vældig godt	Godt	Mindre godt	Dårligt
3. Hvordan synes du, at dit helbred er alt i alt? ..... *(Sæt venligst ét kryds)*	☐	☐	☐	☐	☐

	Meget bedre nu end for ét år siden	Noget bedre nu end for ét år siden	Nogenlunde det samme	Noget dårligere nu end for ét år siden	Meget dårligere nu end for ét år siden
4. Sammenlignet med <u>for ét år siden</u>, hvordan er dit helbred alt i alt nu? ... *(Sæt venligst ét kryds)*	☐	☐	☐	☐	☐

5. De følgende spørgsmål handler om aktiviteter i dagligdagen. Er du på grund af dit helbred begrænset i disse aktiviteter? I så fald, hvor meget?

(Sæt venligst ét kryds i hver linje)

	Ja, meget begrænset	Ja, lidt begrænset	Nej, slet ikke begrænset
a. **Krævende aktiviteter**, som fx løbe, løfte tunge ting, deltage i anstrengende sport	☐	☐	☐
b. **Lettere aktiviteter**, såsom fx at flytte et bord, støvsuge eller cykle	☐	☐	☐
c. At løfte eller bære dagligvarer	☐	☐	☐
d. At gå **flere** etager op ad trapper	☐	☐	☐
e. At gå **én** etage op ad trapper	☐	☐	☐
f. At bøje sig ned eller gå ned i knæ	☐	☐	☐
g. Gå **mere end én kilometer**	☐	☐	☐
h. Gå **nogle hundrede meter**	☐	☐	☐
i. Gå **100 meter**	☐	☐	☐
j. Gå i bad eller tage tøj på	☐	☐	☐

6. Hvor stor en del af tiden inden for de <u>sidste 4 uger</u> har du haft følgende problemer med dit arbejde eller andre daglige aktiviteter <u>på grund af dit fysiske helbred</u>?

(Sæt venligst ét kryds i hver linje)

	Hele tiden	Det meste af tiden	Noget af tiden	Lidt af tiden	På intet tidspunkt
a. Jeg har skåret ned på den **tid**, jeg bruger på arbejde eller andre aktiviteter	☐	☐	☐	☐	☐
b. Jeg har **nået mindre**, end jeg gerne ville	☐	☐	☐	☐	☐
c. Jeg har været begrænset i hvilken **slags** arbejde eller andre aktiviteter, jeg har kunnet udføre	☐	☐	☐	☐	☐
d. Jeg har haft besvær med at udføre mit arbejde eller andre aktiviteter (fx krævede det en ekstra indsats)	☐	☐	☐	☐	☐

7. Hvor stor en del af tiden inden for de sidste 4 uger har du haft følgende problemer med dit arbejde eller andre daglige aktiviteter på grund af følelsesmæssige problemer?

(Sæt venligst ét kryds i hver linje)

	Hele tiden	Det meste af tiden	Noget af tiden	Lidt af tiden	På intet tidspunkt
a. Jeg har skåret ned på den **tid**, jeg bruger på arbejde eller andre aktiviteter	☐	☐	☐	☐	☐
b. Jeg har **nået mindre**, end jeg gerne ville	☐	☐	☐	☐	☐
c. Jeg har været begrænset i hvilken **slags** arbejde eller andre aktiviteter, jeg har kunnet udføre	☐	☐	☐	☐	☐

8. Inden for de sidste 4 uger, hvor meget har dit fysiske helbred eller følelsesmæssige problemer vanskeliggjort din kontakt med familie, venner, naboer eller andre?

(Sæt venligst ét kryds)

Slet ikke	Lidt	Noget	En hel del	Virkelig meget
☐	☐	☐	☐	☐

9. Hvor stærke fysiske smerter har du haft i de sidste 4 uger?

(Sæt venligst ét kryds)

Ingen smerter	Meget lette smerter	Lette smerter	Middelstærke smerter	Meget stærke smerter
☐	☐	☐	☐	☐

10. Inden for de sidste 4 uger, hvor meget har fysiske smerter vanskeliggjort dit daglige arbejde (både arbejde udenfor hjemmet og husarbejde)?

(Sæt venligst ét kryds)

Slet ikke	Lidt	Noget	En hel del	Virkelig meget
☐	☐	☐	☐	☐

11. De næste spørgsmål handler om, hvordan du har haft det i de sidste 4 uger. Vælg det svar, som bedst beskriver, hvordan du har haft det.

I de sidste 4 uger... *(Sæt venligst ét kryds i hver linje)*	Hele tiden	En stor del af tiden	En del af tiden	Lidt af tiden	På intet tidspunkt
a. Har du følt dig veloplagt og fuld af liv?...	☐	☐	☐	☐	☐
b. Har du været meget nervøs?	☐	☐	☐	☐	☐
c. Har du været så langt nede at intet kunne muntre dig op?	☐	☐	☐	☐	☐
d. Har du følt dig rolig og afslappet?	☐	☐	☐	☐	☐
e. Har du været fuld af energi?	☐	☐	☐	☐	☐
f. Har du følt dig trist til mode?	☐	☐	☐	☐	☐
g. Har du følt dig udslidt?	☐	☐	☐	☐	☐
h. Har du været glad og tilfreds?	☐	☐	☐	☐	☐
i. Har du følt dig træt?	☐	☐	☐	☐	☐

12. Inden for de sidste 4 uger, hvor stor en del af tiden har dit fysiske helbred eller følelsesmæssige problemer gjort det vanskeligt at se andre mennesker (fx besøge venner, slægtninge osv.)?
(Sæt venligst ét kryds)

Hele tiden	Det meste af tiden	Noget af tiden	Lidt af tiden	På intet tidspunkt
☐	☐	☐	☐	☐

13. De følgende spørgsmål handler om, hvordan du har sovet i <u>de sidste 4 uger</u>.
(Sæt venligst ét kryds i hver linje)

	Hele tiden	En stor del af tiden	En del af tiden	Lidt af tiden	På intet tidspunkt
a. Hvor tit har du sovet dårligt og uroligt?	☐	☐	☐	☐	☐
b. Hvor tit har du haft svært ved at falde i søvn?	☐	☐	☐	☐	☐
c. Hvor tit er du vågnet for tidligt uden at kunne falde i søvn igen?	☐	☐	☐	☐	☐
d. Hvor tit er du vågnet flere gange og haft svært ved at falde i søvn igen?.....	☐	☐	☐	☐	☐

Spørgsmål om forventning og tiltro

De følgende spørgsmål handler ikke om dit helbred. De handler om dine forventninger og tiltro til din evne til at håndtere din gigt i dagligdagen (fx gennem medicinering, øvelser eller ændringer i dine aktiviteter)

14. Forventer du, at du kan formindske dine smerter væsentligt?
(Sæt venligst ét kryds)

Det er jeg meget usikker på, om jeg kan									Det er jeg helt sikker på, at jeg kan
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
1	2	3	4	5	6	7	8	9	10

15. Forventer du, at du kan forhindre dine gigtsmerter i at forstyrre din søvn?
(Sæt venligst ét kryds)

Det er jeg meget usikker på, om jeg kan									Det er jeg helt sikker på, at jeg kan
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
1	2	3	4	5	6	7	8	9	10

16. Forventer du, at du kan håndtere dine gigtsmerter, så du kan gøre de ting, du gerne vil?
(Sæt venligst ét kryds)

Det er jeg meget usikker på, om jeg kan									Det er jeg helt sikker på, at jeg kan
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
1	2	3	4	5	6	7	8	9	10

17. Forventer du, at du kan tilpasse dine aktiviteter, sådan at du kan være aktiv uden at forværre gigten?
(Sæt venligst ét kryds)

Det er jeg meget usikker på, om jeg kan									Det er jeg helt sikker på, at jeg kan
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10

18. Forventer du, at du kan håndtere trætheden fra din gigt, så den ikke griber ind i det du ønsker at gøre?
(Sæt venligst ét kryds)

Det er jeg meget usikker på, om jeg kan									Det er jeg helt sikker på, at jeg kan
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10

19. Forventer du, at du selv kan gøre noget for at få det bedre, hvis du er trist?
(Sæt venligst ét kryds)

Det er jeg meget usikker på, om jeg kan									Det er jeg helt sikker på, at jeg kan
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10

20. Sammenlignet med andre personer med gigt, hvor stor er din tiltro til, at du kan håndtere dine smerter under dine daglige gøremål?
(Sæt venligst ét kryds)

Ringe tiltro									Stor tiltro
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10

21. Forventer du, at du kan håndtere frustrationen ved at have en gigtsygdom?
(Sæt venligst ét kryds)

Det er jeg meget usikker på, om jeg kan									Det er jeg helt sikker på, at jeg kan
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10

Spørgsmål om dig selv og din familie

	Ja	Nej
22. Bor du sammen med en ægtefælle/samlever?	☐	☐

23. Har du hjemmeboende børn?
(medtag både dine egne børn og evt ægtefælle/samlevers børn som bor hos jer hele tiden eller noget af tiden)
(Sæt venligst ét kryds).....

Nej	Ja, 1 barn	Ja, 2 børn	Ja, 3 eller flere børn
☐	☐	☐	☐

24. Hvis du har hjemmeboende børn, hvor gammelt er det YNGSTE hjemmeboende barn? ..... ⌊_⌊_⌋ År

25. Ryger du?
(Sæt venligst ét kryds) .....

Ja, Dagligt	Ja, af og til	Har røget, men ryger ikke mere	Har aldrig røget
☐	☐	☐	☐

26. Hvis du ryger, hvor meget ryger du så om dagen i gennemsnit? ..... ⌊_⌊_⌋ Cigaretter/cigarer/cerutter/ pibestop per dag

27. Hvor ofte motionerer du i mindst en halv time? (dvs. du får øget puls og bliver forpustet)
(Sæt venligst ét kryds)

3 eller flere gange om ugen	1 - 2 gange om ugen	1 - 2 gange om måneden	Træner ikke regelmæssigt	Kan ikke træne pga. skavanker / handicap
☐	☐	☐	☐	☐

Din beskæftigelse

28. Hvad er din hovedbeskæftigelse i øjeblikket?
Dvs. den du bruger mest tid på.
(Sæt venligst ét kryds)

Du er i arbejde:

1. Lønmodtager ..... ☐
2. Lønmodtager med ledelsesansvar ..... ☐ Hvor mange underordnede har du? ⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋
3. Selvstændig erhvervsdrivende (fx selvstændig landmand, anden selvstændig virksomhed eller medhjælpende ægtefælle) ..... ☐ Hvor mange ansatte har du? ⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋
4. Sygemeldt fra arbejde ..... ☐

Du er IKKE i arbejde:

5. Sygemeldt, ikke i arbejde ..... ☐
6. Under uddannelse (skoleelev/studerende uden fritidsjob) ..... ☐
7. Under revalidering ..... ☐
8. Hjemmegående ..... ☐
9. På orlov ..... ☐
10. Arbejdsledig ..... ☐
11. På kontanthjælp ..... ☐
12. På efterløn, pensionist ..... ☐
13. Andet, der ikke er arbejde ..... ☐

Hvis du er i arbejde, og dermed har valgt en af kategorierne 1-4, så gå venligst videre med at besvare resten af spørgeskemaet.

Hvis du IKKE er i arbejde, og dermed har valgt en af kategorierne 5-13, skal du ikke besvare flere spørgsmål. Send venligst det udfyldte spørgeskema retur i den vedlagte svarkuvert. Vi takker for hjælpen.

Spørgsmål om din hovedbeskæftigelse

29. Hvor længe har du været på din nuværende arbejdsplads? ..... ⌊_⌋⌊_⌋ År ⌊_⌋⌊_⌋ Måneder

30. Hvor mange ansatte er der på din arbejdsplads?

(Hvis din virksomhed har underafdelinger med forskellige adresser, så svar for den adresse hvor du selv arbejder - *sæt venligst ét kryds*)

1-4	5-9	10-19	20-49	50-99	100-249	250-499	500 eller derover
☐	☐	☐	☐	☐	☐	☐	☐

31. Hvad er den aftalte ugentlige arbejdstid i din hovedbeskæftigelse?

(Skriv venligst den aftalte arbejdstid ifølge overenskomst eller anden aftale - fx 37 timer per uge. Hvis du er selvstændig eller ikke har en aftalt ugentlig arbejdstid, så spring spørgsmålet over. Hvis du er i flexjob, så svar det antal timer du er ansat til, fraset flexjob) ..... ⌊_⌋⌊_⌋,⌊_⌋

32. Hvor mange timer arbejder du rent faktisk om ugen i din hovedbeskæftigelse?

(Skriv venligst gennemsnit per uge i det sidste år) ..... ⌊_⌋⌊_⌋,⌊_⌋

33. Hvis du har et bijob, hvor mange timer arbejder du så rent faktisk om ugen i dit bijob?

(Skriv venligst gennemsnit per uge i det sidste år) ..... ⌊_⌋⌊_⌋,⌊_⌋

34. På hvilket tidspunkt af døgnet arbejder du sædvanligvis i din hovedbeskæftigelse?

(Sæt venligst ét kryds)

Fast dagarbejde (overvejende mellem kl. 06 og 18)	Fast aftenarbejde (overvejende mellem kl.15 og 24)	Fast natarbejde (overvejende mellem kl.22 og 06)	Skiftende arbejdstider	Andet
☐	☐	☐	☐	☐

Hvis andet, skriv: _____

35. Foregår dit erhvervsarbejde helt eller delvis i dit eget hjem?
(Sæt venligst ét kryds)

Næsten hele tiden	Ca. 3/4 af tiden	Ca. 1/2 af tiden	Ca. 1/4 af tiden	Sjældent/ meget lidt	Aldrig
☐	☐	☐	☐	☐	☐

36. Er der, på grund af din gigt, iværksat særlige ordninger for at fastholde dig i arbejde?
(Sæt venligst ét kryds i hver linje)

	Ja, ordningen løber fortsat	Før i tiden, men ikke mere	Nej	Ved ikke
a. Er du i flexjob?	☐	☐	☐	☐
b. Er du i § 56 ordning? (Kommunen betaler sygefravær fra dag 1)	☐	☐	☐	☐

	Ja	Nej	Ved ikke
c. Har du modtaget træning i at udføre dit arbejde på en anden måde?	☐	☐	☐
d. Har du fået andre arbejdsopgaver på samme arbejdsplads?	☐	☐	☐
e. Har du fået formel uddannelse til et andet arbejde, på grund af din gigt?	☐	☐	☐
f. Har du skiftet arbejde, på grund af din gigt?	☐	☐	☐
g. Andre foranstaltninger?	☐	☐	☐

Skriv hvilke: _____

37. Anvender du en af følgende foranstaltninger på grund af din gigt?
(Sæt venligst ét kryds i hver linje)

	Anvender nu	Har tidligere anvendt	Har aldrig anvendt
a. Personlig assistance arbejdsmæssigt?	☐	☐	☐
b. Hjælpemidler / arbejdsredskaber?	☐	☐	☐
c. Speciel indretning af arbejdspladsen?	☐	☐	☐
d. Andre aftaler om aflastning?	☐	☐	☐
e. Andet?	☐	☐	☐

Beskriv hvad:

_____

Spørgsmål om arbejdsstillinger

38. Hvordan vil du beskrive din fysiske aktivitet i din hovedbeskæftigelse?
(Sæt venligst ét kryds)

Mest **stillesiddende** arbejde, som ikke kræver fysisk anstrengelse	Mest **stående eller gående** arbejde, som ikke kræver fysisk anstrengelse	**Stående eller gående** arbejde med en del løfte- eller bærearbejde	Tungt eller hurtigt arbejde, som er **fysisk anstrengende**
☐	☐	☐	☐

39. Medfører dit arbejde at …
(Sæt venligst ét kryds i hver linje)

	Næsten hele tiden	Ca. 3/4 af tiden	Ca. 1/2 af tiden	Ca. 1/4 af tiden	Sjældent/ meget lidt	På intet tidspunkt
a. Du sidder samme sted?	☐	☐	☐	☐	☐	☐
b. Du står samme sted?	☐	☐	☐	☐	☐	☐
c. Du arbejder med ryggen kraftigt foroverbøjet uden at støtte med hænder og arme?	☐	☐	☐	☐	☐	☐
d. Du vrider eller bøjer i ryggen?	☐	☐	☐	☐	☐	☐
e. Du har armene løftet i eller over skulderhøjde?	☐	☐	☐	☐	☐	☐
f. Du gør de samme fingerbevægelser mange gange i minuttet (fx indtastningsarbejde)?	☐	☐	☐	☐	☐	☐
g. Du gør de samme armbevægelser mange gange i minuttet (fx pakkearbejde, montering, maskinfødning, udskæring)?	☐	☐	☐	☐	☐	☐
h. Du sidder på hug eller ligger på knæ, når du arbejder?	☐	☐	☐	☐	☐	☐
i. Du er udsat for træk?	☐	☐	☐	☐	☐	☐
j. Du er udsat for kulde?	☐	☐	☐	☐	☐	☐
k. Hvor stor en del af din arbejdstid skubber eller trækker du noget?	☐	☐	☐	☐	☐	☐
l. Hvor stor en del af din arbejdstid bærer eller løfter du noget?	☐	☐	☐	☐	☐	☐

Spørgsmål om din arbejdsevne

40. Hvordan vurderer du din nuværende arbejdsevne i forhold til …
(Sæt venligst ét kryds i hver linje)

	Fremragende	Særdeles god	God	Nogenlunde	Dårlig
a. De fysiske krav i dit arbejde?	☐	☐	☐	☐	☐
b. De mentale krav i dit arbejde?	☐	☐	☐	☐	☐

41. Hvor mange point vil du give din nuværende arbejdsevne, hvis din arbejdsevne, når den er bedst, svarer til 10 point? (0 betyder at du for øjeblikket er ude af stand til at arbejde)
(Sæt venligst ét kryds på skalaen).....

Fuldstændig ude af stand til at arbejde									Arbejdsevne, når den er bedst
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
1	2	3	4	5	6	7	8	9	10

42. Vil du sige, at din arbejdsevne er nedsat på grund af sygdom, ulykke eller slid?
(Sæt venligst ét kryds) .....

Ja, i høj grad	Ja, I nogen grad	Nej, ikke særligt	Nej, slet ikke
☐	☐	☐	☐

43. Hvis du tænker på dit helbred, tror du så, at du er i stand til at udføre dit job om 2 år?

	Nej, helt utænkeligt	Nej, sandsynligvis ikke	Ja, sandsynligvis	Ja, helt sikkert
(Sæt venligst ét kryds)	☐	☐	☐	☐

Spørgsmål om tilfredshed og indflydelse i arbejdet

44. Hvor tilfreds er du med dit job som helhed, alt taget i betragtning?
(Sæt venligst ét kryds)

Meget tilfreds	Tilfreds	Utilfreds	Meget utilfreds
☐	☐	☐	☐

45. Tilfredshed og indflydelse.
(Sæt venligst ét kryds i hver linje)

	Altid	Ofte	Somme tider	Sjældent	Aldrig/ næsten aldrig
a. Har du stor indflydelse på beslutninger om dit arbejde?	☐	☐	☐	☐	☐
b. Har du indflydelse på mængden af dit arbejde?	☐	☐	☐	☐	☐
c. Har du indflydelse på, HVAD du laver på dit arbejde?	☐	☐	☐	☐	☐
d. Har du indflydelse på, hvem du arbejder sammen med?	☐	☐	☐	☐	☐
e. Har du indflydelse på placeringen af din arbejdstid?	☐	☐	☐	☐	☐
f. Skal du tage stilling til andre menneskers personlige problemer i dit arbejde?.....	☐	☐	☐	☐	☐
g. Kan du bestemme hvornår du holder pauser?	☐	☐	☐	☐	☐
h. Hvis du har brug for at forlade arbejdspladsen, kan du så gå i en halv time i et privat ærinde uden at få særlig tilladelse?	☐	☐	☐	☐	☐
i. Kan du gå hen til en kollega for at snakke? ..	☐	☐	☐	☐	☐

46. De følgende spørgsmål handler om situationer, hvor du har brug for hjælp eller støtte i dit arbejde. Hvis du ikke har en kollega eller overordnet/leder, bedes du sætte kryds i "ikke relevant".

(Sæt venligst ét kryds i hver linje)

	Altid	Ofte	Somme tider	Sjældent	Aldrig/ næsten aldrig	Ikke relevant
a. Hvor ofte er dine kolleger villige til at lytte til dine problemer med arbejdet?	☐	☐	☐	☐	☐	☐
b. Hvor ofte taler dine kolleger med dig om, hvor godt du udfører dit arbejde?	☐	☐	☐	☐	☐	☐
c. Er der en god stemning mellem dig og dine kolleger?	☐	☐	☐	☐	☐	☐
d. Er der et godt samarbejde blandt kollegerne på din arbejdsplads?	☐	☐	☐	☐	☐	☐
e. Føler du dig som en del af et fællesskab på din arbejdsplads?	☐	☐	☐	☐	☐	☐

47. De følgende spørgsmål handler om dit forhold til din nærmeste overordnede. Hvis du ikke har en overordnet/leder, bedes du sætte kryds i "ikke relevant".

(Sæt venligst ét kryds i hver linje)

	Altid	Ofte	Somme tider	Sjældent	Aldrig/ næsten aldrig	Ikke relevant
a. Hvor ofte er din nærmeste overordnede villig til at lytte til dine problemer med arbejdet?	☐	☐	☐	☐	☐	☐
b. Hvor ofte får du hjælp og støtte fra din nærmeste overordnede? ..	☐	☐	☐	☐	☐	☐
c. Hvor ofte taler din nærmeste overordnede med dig om, hvor godt du udfører dit arbejde?	☐	☐	☐	☐	☐	☐

48. I hvor høj grad kan man sige, at den nærmeste ledelse på din arbejdsplads -

(Sæt venligst ét kryds i hver linje)

	I meget høj grad	I høj grad	Delvist	I ringe grad	I meget ringe grad	Ikke relevant
a. sørger for, at den enkelte medarbejder har gode udviklingsmuligheder?	☐	☐	☐	☐	☐	☐
b. prioriterer trivslen på arbejdspladsen højt?	☐	☐	☐	☐	☐	☐
c. er god til at planlægge arbejdet? ...	☐	☐	☐	☐	☐	☐
d. kommunikerer en klar og positiv vision for fremtiden?	☐	☐	☐	☐	☐	☐
e. opmuntrer medarbejderne til at anskue problemerne på nye måder?..	☐	☐	☐	☐	☐	☐
f. giver klart udtryk for sine værdier og efterlever dem?	☐	☐	☐	☐	☐	☐

49. Er du bekymret for at der sker dig noget af følgende …

(Sæt venligst ét kryds i hver linje)

	I meget høj grad	I høj grad	Delvist	I ringe grad	I meget ringe grad	Er selvstændig
a. At du bliver arbejdsløs?	☐	☐	☐	☐	☐	☐
b. At du vil få svært ved at finde et nyt job, hvis du bliver arbejdsløs?	☐	☐	☐	☐	☐	☐

Arbejdspladsen som helhed

50. De næste spørgsmål handler ikke om dit eget job, men om din arbejdsplads som helhed.

(Sæt venligst ét kryds i hver linje)

	I meget høj grad	I høj grad	Delvist	I ringe grad	I meget ringe grad
a. Stoler ledelsen på, at medarbejderne gør et godt stykke arbejde?	☐	☐	☐	☐	☐
b. Kan man stole på de udmeldinger, der kommer fra ledelsen?	☐	☐	☐	☐	☐
c. Kan de ansatte give udtryk for deres meninger og følelser?	☐	☐	☐	☐	☐
d. Bliver konflikter løst på en retfærdig måde?	☐	☐	☐	☐	☐
e. Bliver man anerkendt for et godt stykke arbejde?	☐	☐	☐	☐	☐
f. Bliver alle forslag fra de ansatte behandlet seriøst af ledelsen?	☐	☐	☐	☐	☐
g. Bliver arbejdsopgaverne fordelt på en retfærdig måde?	☐	☐	☐	☐	☐
h. Er der plads til ældre medarbejdere?	☐	☐	☐	☐	☐
i. Er der plads til ansatte med forskellige skavanker og handicaps?	☐	☐	☐	☐	☐

Du er nu færdig med spørgeskemaet. Returner venligst skemaet i vedlagte svarkuvert. Mange tak for hælpen.

Hvis du har kommentarer til skemaet, eller andre kommentarer, så skriv dem venligst på næste side.

51. Dine eventuelle kommentarer kan skrives her:

_____

_____

_____

_____

_____

GRADUATE SCHOOL OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

DECLARATION OF CO-AUTHORSHIP

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Rheumatoid Arthritis and Work - Risk and Risk Factors for Long Term Sickness Absence, Unemployment, and Disability Pension

This declaration concerns the following article:
Work Environmental Risk Factors for Long Term Sickness Absence in Patients with Rheumatoid Arthritis - A Two Year Prospective Cohort Study

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	C
2. Planning of the experiments and methodology design, including selection of methods and method development	C
3. Involvement in the experimental work	C
4. Presentation, interpretation and discussion in a journal article format of obtained data	C

**Benchmark scale of the PhD student's contribution to the article*		
A. refers to:	*Has contributed to the co-operation*	*0-33 %*
B. refers to:	*Has contributed considerably to the co-operation*	*34-66 %*
C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

Signature of the co-authors:			
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04 01 2016	Merete Lund Hetland	professor, MD, PhD,	Merete Lund Hetland
04 01 2016	Jacob Pedersen	Ph.D	Jacob Pedersen

04 01 2016	Mikkel Østergaard	Ostergaard, professor Ph.D.,	
04 01 2016	Jakob Bue Bjørner	,professor, Ph.D	

Signature of the PhD student and the principal supervisor:	
Date: 04/01/2016 PhD student:	Date: 04/01/2016 Principal supervisor:

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Principal supervisor	Merete Lund Hetland

Title of PhD thesis:
Rheumatoid Arthritis and Work - Risk and Risk Factors for Long Term Sickness Absence, Unemployment, and Disability Pension

This declaration concerns the following article:
Impact of Rheumatoid Arthritis on Long Term Sickness Absence in 1994-2011: A Danish Cohort Study.

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	C
2. Planning of the experiments and methodology design, including selection of methods and method development	C
3. Involvement in the experimental work	C
4. Presentation, interpretation and discussion in a journal article format of obtained data	C

**Benchmark scale of the PhD student's contribution to the article*		
A. refers to:	*Has contributed to the co-operation*	*0-33 %*
B. refers to:	*Has contributed considerably to the co-operation*	*34-66 %*
C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

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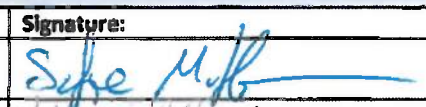
04 01 2016	Sofie Mandrup Hansen	Ph.D. student, MSc	
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